Role of Dopamine D_2 Receptors for Antipsychotic Activity

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Contents

Abstract This review summarizes the current state of knowledge regarding the proposed mechanisms by which antipsychotic agents reduce the symptoms of schizophrenia while giving rise to adverse side effects. The first part summarizes the contribution of neuroimaging studies to our understanding of the neurochemical substrates of schizophrenia, putting emphasis on direct evidence suggestive of a presynaptic rather than a postsynaptic dysregulation of dopaminergic neurotransmission in this disorder. The second part addresses the role of D_2 and non-D_2 receptor blockade in the treatment of schizophrenia and highlights a preponderant role of D_2 receptors in the mechanism of antipsychotic action. Neuroimaging studies have defined a narrow, but optimal, therapeutic window of 65–78 %

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D_2 receptor blockade within which most antipsychotics achieve optimal clinical efficacy with minimal side effects. Some antipsychotics though do not conform to that therapeutic window, notably clozapine. The reasons for its unexcelled clinical efficacy despite subthreshold levels of D_2 blockade are unclear and current theories on clozapine's mechanisms of action are discussed, including transiency of its D_2 receptor blocking effects or preferential blockade of limbic D_2 receptors. Evidence is also highlighted to consider the use of extended antipsychotic dosing to achieve transiency of D_2 blockade as a way to optimize functional outcomes in patients. We also present some critical clinical considerations regarding the mechanisms linking dopamine disturbance to the expression of psychosis and its blockade to the progressive resolution of psychosis, keeping in perspective the speed and onset of antipsychotic action. Finally, we discuss potential novel therapeutic strategies for schizophrenia.

Keywords Schizophrenia • Antipsychotic drugs • Dopamine receptor • D_2 blockade • PET imaging

1 Introduction

Schizophrenia is a chronic and disabling disease afflicting nearly 1 % of the general population (Perala et al. 2007). Clinically, the disorder manifests with a large variety of symptoms that fall into three categories: positive, negative, and cognitive (Kapur and Mamo 2003; Lieberman et al. 2005). Positive symptoms typically reflect a distortion of normal functions that are regarded as manifestations of psychosis and include hallucinations, delusions, and disorganized thoughts. Negative symptoms are associated with a diminution or loss of normal emotions and behaviors and manifest as affective blunting, social isolation, poverty of speech, anhedonia, and avolition. Cognitive symptoms relate to abnormal thought processes and manifest as deficits in attention, working memory, and executive functioning. Schizophrenia appears to be a polygenic disorder in which genetic factors combined with abnormalities in early brain development (including apoptosis, synaptic pruning, and disruption of neuronal migration) may confer a constitutional vulnerability to the disease (Walker et al. 2004). Subsequent environmental insults (including exposure to infectious, toxic, or traumatic insults and stress in utero or during childhood) may unmask this vulnerability and trigger overt manifestation of schizophrenia (Tsuang 2000). Within this framework, dysregulations of the dopamine (DA) neurotransmitter system have been most intimately associated with the pathophysiology of schizophrenia. Moreover, all antipsychotics act by blocking DA receptors, indicating that opposing DA signaling is central for alleviating psychotic symptoms. It is this aspect of the illness that is the focus of this review, with special attention given to the DA D_2 receptors.

1.1 Role of Dopamine in the Pathophysiology of Schizophrenia

For almost 50 years, schizophrenia research has focused on dopaminergic signaling as a key feature in the treatment and etiology of the disease. In particular, the original "DA hypothesis" posits a hyperdopaminergic function in brain as a possible cause of the illness (van Rossum 1966). This hypothesis was initially based on several lines of indirect evidence. First, exposure to psychostimulants such as amphetamine, which increase brain DA activity, can induce psychotic symptoms in normal individuals and worsen psychotic symptoms in schizophrenia patients (Connell 1958), whereas drugs known as DA depleters, such as reserpine, alleviate them (Carlsson et al. 1957). Further evidence for a DA hyperfunction in schizophrenia came from research on the mechanism of antipsychotic action. Notably, early work from Carlsson and Lindqvist (1963) indicated that central DA receptor blockade by chlorpromazine and haloperidol was the mechanism of their antipsychotic action. Actually, all antipsychotics act by blocking DA D_2 receptors and there is a tight correlation between the clinical potency of these drugs and their pharmacological potency at blocking D_2 receptors (Seeman and Lee 1975). This observation leads to the dominant theory that the positive symptoms of the illness are directly related to a subcortical dopaminergic overactivity, which may be due to an excess of DA itself or to hypersensitive D_2 receptors.

1.1.1 Dopamine Receptor Studies in Schizophrenia

Since all current antipsychotics block D_2 receptors, there has been tremendous interest in whether the expression of those receptors is altered in schizophrenia. While early postmortem studies showed a D_2 elevation in schizophrenia (Lee et al. 1978; Seeman et al. 1984), the finding that antipsychotic treatment per se increased striatal D_2 receptor density in experimental animals (Burt et al. 1977; Owen et al. 1980) raised the concern that the D_2 receptor elevation observed in schizophrenia was the consequence of prior drug treatment (Seeman 1987). With the advent of positron emission tomography (PET) and single positron emission computed tomography (SPECT) imaging technologies came the opportunity to investigate D_2 receptor availability in drug-naive patients in vivo. Initial imaging studies in drug-naïve or drug-free patients remained inconclusive, with some studies reporting higher than normal striatal D_2 receptor density and others showing no difference from controls (Farde et al. 1987; Hietala et al. 1994; Pilowsky et al. 1994; Tune et al. 1993; Wong et al. 1986). Since these initial reports, other studies have followed and failed to detect significant alteration in striatal D_2 receptors in drug-naïve schizophrenic patients (Buchsbaum et al. 2006; Glenthoj et al. 2006; Lomena et al. 2004; Nordstrom et al. 1995; Talvik et al. 2006; Yang et al. 2004). More recently, meta-analyses examining the aggregate results of previous D_2 receptor imaging studies revealed that there is an increase in striatal D_2 receptor density in schizophrenia, although modest (around 13–14 %), that is independent of

the effects of antipsychotic treatment (Kestler et al. 2001; Laruelle 1998; Zakzanis and Hansen 1998). Striatal D_1 receptor density appears unaffected (Abi-Dargham et al. 2002; Karlsson et al. 2002). With the recent availability of high-affinity PET radiotracers, there has been a tremendous interest in investigating extrastriatal dopamine D_2 receptors in schizophrenia. Several PET imaging studies with high-affinity ligands have found consistently lower D_2 receptor densities (in the 20 % range) in the thalamus, as well as in the amygdala, cingulate gyrus, and temporal cortices (Buchsbaum et al. 2006; Kessler et al. 2009; Suhara et al. 2002; Talvik et al. 2003), thus providing no support for a D_2 receptor supersensitivity in schizophrenia. It has been proposed that while there may not be an absolute change in the overall number of D_2 receptors, a higher proportion of D_2 receptors with functional high affinity for DA may explain hyperdopaminergia (Seeman et al. 2005). However, a recent clinical study to investigate levels of those high-affinity state D_2 receptors found no difference between schizophrenia patients and controls (Graff-Guerrero et al. 2009b). Thus, despite extensive efforts over the past 40 years, no convincing evidence has emerged yet that unequivocally points to a D_2 receptor abnormality in schizophrenia.

Dopamine Presynaptic Dysregulation in Schizophrenia

Contrasting with studies looking at postsynaptic D_2 receptors, PET imaging of the presynaptic aspect of DA neurotransmission has provided converging evidence for the existence of presynaptic dopamine overactivity in schizophrenia. In vivo presynaptic DA activity has been investigated using several methods carried out to study particular elements of DA function. The first method involved the use of the DA precursor analog radioligand [^{18}F]DOPA, whose accumulation in brain represents the activity of the aromatic acid decarboxylase enzyme and the storage capacity of presynaptic DA (Brown et al. 1999) and is generally considered as an index of DA synthesis. The other methods take advantage of the well-described in vivo competing effect exerted by endogenous DA on the binding of some D_2 radiotracers to index evoked DA release or baseline levels of extracellular DA (Ginovart 2005; Laruelle 2000). Without a few exceptions (Dao-Castellana et al. 1997; Elkashef et al. 2000), all studies investigating presynaptic dopamine metabolism indicate a heightened presynaptic capacity of DA synthesis in schizophrenia (Hietala et al. 1995, 1999; Kumakura et al. 2007; Lindstrom et al. 1999; McGowan et al. 2004; Meyer-Lindenberg et al. 2002; Nozaki et al. 2009; Reith et al. 1994) that might be used as an index to discriminate patients from controls (Bose et al. 2008). Interestingly, it has recently been demonstrated that patients with prodromal symptoms of schizophrenia also show elevated striatal DA synthesis (Howes et al. 2009), indicating that presynaptic DA abnormalities predate the onset of illness and are thus likely related to the cause rather than being a consequence of the disorder. Further evidence for an elevated DA availability in schizophrenia comes from studies showing an exaggerated release of DA in the striatum of schizophrenic patients both at basal conditions (Abi-Dargham et al.

2000) and in response to amphetamine (Abi-Dargham et al. 1998; Bertolino et al. 2000; Breier et al. 1997; Laruelle et al. 1996). Taken together, these data suggest that an increased presynaptic capacity of DA synthesis and release may constitute part of the dysfunctional neural connectivity underlying schizophrenia and may be the concurring proximate causes of psychoses. In contrast, a DA hypofunction may prevail in the neocortex (Grace 1991). A reconceptualization of the original DA hypothesis of schizophrenia followed that refined the notion of a global hyperdopaminergia to a cortical/subcortical imbalance of DA tone in brain (Davis et al. 1991; Howes and Kapur 2009). According to this new hypothesis, positive symptoms of the disorder would result from a subcortical hyperdopaminergia, whereas negative symptoms and cognitive deficits would result from a concomitant hypodopaminergia in frontal cortex.

2 Mechanism of Antipsychotic Action

2.1 Antipsychotic Treatment

Antipsychotics fall into two classes, typical and atypical, which differ in their side-effect and receptor binding profiles. Typical antipsychotics such as haloperidol and chlorpromazine have been available since the 1950s and belong to the first generation of antipsychotics drugs. Typical antipsychotics are effective in treating both the positive and negative symptoms of schizophrenia, although the degree of improvement of negative symptoms is usually less than that of positive symptoms (Goldberg 1985). Besides their therapeutic efficacy, first-generation agents cause a variety of undesirable adverse events, including acute (parkinsonism, akathisia, dystonia) and later-onset (tardive dyskinesia; TD) extrapyramidal side effects (EPS) and a propensity to cause prolactin elevation. In addition to EPS, typical antipsychotics also cause subjective side effects that are characterized by symptoms of dysphoria/anhedonia, depressed mood, and a slowed mentation (Marder 2005; Voruganti and Awad 2004). These subjective effects can manifest within the first few days of treatment (see reviews in Awad and Voruganti 2005; Lambert et al. 2003) and distinguishing them from the primary negative symptoms of schizophrenia can be difficult (Lewander 1994; Schooler 1994). Subjective distress associated with motor and subjective side effects of typical antipsychotics has a negative impact on patient's quality of life and well-being and can lead to noncompliance (Naber et al. 2005; Robinson et al. 2002), and subsequent relapse (Morken et al. 2008; Robinson et al. 1999). Moreover, the lack of response in 20–40 % of patients with schizophrenia represents another limitation of typical antipsychotic for adequate treatment of the disease (Hellewell 1999).

Atypical (or second-generation) antipsychotics are comparable to typical agents with respect to efficacy in reducing positive symptoms but have been associated with a lower risk to cause EPS (Correll and Schenk 2008; Haro and Salvador-Carulla 2006). However, there are considerable variations in the

propensity of individual atypical agents to cause EPS, with some atypical drugs, such as clozapine and quetiapine, showing no greater EPS than placebo across their full dosage range (Arvanitis and Miller 1997; Goldstein 2000) and some others, such as risperidone and olanzapine, showing increased risk with increased dosage (Lemmens et al. 1999). Studies comparing atypical versus typical agents with respect to EPS risk have commonly used haloperidol, a highly potent typical agent comparator that carries a high liability for EPS, particularly at the relatively high doses used—and not surprisingly in these studies atypicals showed a substantial advantage in terms of EPS. However, large efficacy studies such as CATIE (Rosenheck et al. 2006) and CUtLASS (Jones et al. 2006), which have used moderate doses of midpotency typical antipsychotics such as perphenazine and sulpiride, show that it is possible to get equivalent clinical efficacy with typical antipsychotics at doses that do not confer higher risk for EPS. Thus, while it is generally agreed that atypical antipsychotics have, overall, a more favorable side-effect profile than typical agents, it is uncertain whether this superiority can be sustained when controlling for antipsychotic potency and dose inequities. Similarly, and contrary to common thinking that atypicals have improved efficacy against negative symptoms, meta-analyses revealed rather moderate advantage, if any, of atypical versus typical drugs in the treatment of negative symptoms (Carman et al. 1995; Davis et al. 2003; Leucht et al. 1999, 2009). Several studies even indicate that typical and atypical drugs can be equally effective in this domain (Arvanitis and Miller 1997; Buchanan et al. 1998; Copolov et al. 2000; Leucht et al. 1999; Möller et al. 2008). It has been suggested that the apparent superior efficacy of atypical versus typical drugs may only relate to the relative absence of confounding, secondary negative symptoms with atypical drugs due to use of a high-dose comparator, haloperidol (Kapur and Remington 2001a). Interestingly, the meta-analysis by Leucht et al. (2009) demonstrated that when compared with midpotency typical antipsychotics or moderate doses of haloperidol (7.5 or 12 mg per day), some atypical antipsychotics such as aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine are as effective as typical drugs for treatment of negative symptoms, whereas others such as amisulpride, clozapine, olanzapine, and risperidone are superior. Thus, atypical antipsychotics are a heterogeneous group of drugs with regard to efficacy against negative symptoms, and it remains unclear whether this only reflects a different propensity to induce EPS and dysphoria or a primary efficacy against negative symptoms. Atypical antipsychotics may thus offer only modest efficacy advantages over typical drugs. However, because they are less prone to induce secondary negative symptoms, in terms of EPS and dysphoria, than typical antipsychotics, they are associated with improved subjective experience (Lambert et al. 2011) and compliance to treatment (Haro et al. 2009; Möller et al. 2008) and may thus achieve a better overall prognosis. This advantage must be balanced though with the occurrence of other, nonmotor adverse effects, since some atypicals are associated with a higher risk of prolactin elevation and others with metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain (Luft and Taylor 2006; Newcomer 2005).

2.2 *Role of D_2 Receptor Blockade*

Besides exhibiting a different side-effect profile, typical and atypical antipsychotics also differ in their receptor binding profiles, with atypical agents acting through a larger spectrum of receptor types, including DA but also serotonergic, cholinergic, and adrenergic receptors. Nevertheless, all antipsychotics share the common ability to antagonize DA D_2 receptors, albeit with different affinities. Early pharmacological studies have established the existence of a close relationship between the clinical potency of antipsychotic drugs and their affinity for D_2 receptors (Creese et al. 1976; Seeman and Lee 1975), pointing to a role of this DA receptor subtype in antipsychotic action. The lack of such correlation for any other DA receptor subtypes (Seeman 1987) further substantiates the view that antipsychotic effects occur primarily through antagonism at D_2 receptors.

Further evidence for this comes from neuroimaging studies in schizophrenia patients that investigated the relationship between antipsychotic-induced D_2 receptor blockade, clinical efficacy, and occurrence of side effects. With a few exceptions, most antipsychotics are effective when 65 % or more of D_2 receptors are blocked in the striatum, indicating that antipsychotic effect is driven primarily by D_2 antagonism (Farde et al. 1992; Kapur et al. 2000a). Increasing striatal D_2 blockade by increasing antipsychotic dosage does not provide additional antipsychotic efficacy but is associated with an increased risk of adverse side effects. Indeed, D_2 blockade exceeding 72 % and 78 % leads to the emergence of hyperprolactinemia and extrapyramidal motor symptoms (EPS), respectively, underscoring the need to carefully control antipsychotic dosage during treatment to avoid adverse effects. These neuroimaging findings have permitted the definition of an optimal therapeutic window of 65–78 % D_2 receptor blockade within which most antipsychotics achieve optimal efficacy with minimal side effects. Although originally demonstrated with the prototypical typical antipsychotic haloperidol, a similar relationship between D_2 receptor blockade and clinical effects was subsequently confirmed for atypical drugs having low EPS liability. Drugs such as remoxipride, olanzapine, and risperidone induce dose-dependent levels of striatal D_2 receptor blockade but achieve therapeutic efficacy only at doses that cross the 65 % threshold level (Kapur et al. 1998, 1999; Nordstrom et al. 1998). However, these drugs dose-dependently lose their low EPS profile because D_2 blockade crossing the 72–75 % level is associated with the emergence of EPS and sustained hyperprolactinemia (Jauss et al. 1998; Knable et al. 1997). Although both the EPS and prolactin elevation are associated with D_2 receptor blockade, different neuroanatomical pathways mediate these effects. Whereas EPS are mediated through excessive blockade of D_2 receptor in striatum, hyperprolactinemia relates to excessive blockade of D_2 receptors in the anterior pituitary, a structure located outside the blood–brain barrier and accessible to drugs that do not penetrate the brain. Atypical antipsychotics vary considerably with regard to their ability to increase prolactin levels (Kapur and Remington 2001a). Drugs such as amisulpride and sulpiride, which display a limited brain penetration, cause few EPS but have a profound effect

on plasma prolactin concentrations when compared to other atypicals such as quetiapine and olanzapine (O'Connor and Brown 1982; Stanniland and Taylor 2000). This dissociation between the occurrence of EPS and prolactin-elevating effect reflects a differential disposition of the drugs across the blood–brain barrier, resulting in higher levels of D_2 receptor blockade in the pituitary than in the striatum (Kapur et al. 2002). Thus, the different propensity of atypical drugs to induce prolactin elevation at therapeutic doses is critically dependent on their ability to cross the brain–blood barrier and the degree to which they induce differential D_2 receptor blockade in the pituitary versus the striatum. Antagonism at the D_2 receptors thus appears central to both the therapeutic and adverse side effects of antipsychotics. Reducing exaggerated DA function through D_2 receptor blockade in the mesolimbic pathway would underlie the progressive resolution of psychosis, whereas excessive reduction of DA function in the nigrostriatal and tuberoinfundibular pathways would lead to EPS and prolactin elevation, respectively. On the other hand, concurrent blockade of D_2 receptors in the mesocortical pathway, where DA function is already deficient in schizophrenia, may even worsen the negative symptoms and cognitive impairment of the disease.

A second approach in the treatment of schizophrenia is to prevent excessive D_2 receptor activation by the use of D_2 partial agonists. Unlike antagonists, which block D_2 activation by endogenous DA, partial agonists activate D_2 receptors but to a lower degree than endogenous DA. The consequence of D_2 partial activation is thus dependent on the local concentration of endogenous DA. When the receptor is hyperactivated by high levels of DA, competitive partial agonist binding to the receptor will have the effect of reducing that activation whereas the opposite effect ensued when the receptor is hypoactivated because of low levels of endogenous DA (Tamminga 2002). Partial DA agonists are therefore believed to restore the cortical/subcortical imbalance of DA tone in schizophrenia by dampening excessive mesolimbic D_2 stimulation and by restoring deficient mesocortical D_2 stimulation (Tamminga 2002). Moreover, by avoiding excessive nigrostriatal D_2 inactivation, a partial D_2 agonist would have a low propensity to cause EPS and prolactin elevation. Aripiprazole, the first successful D_2 partial agonist to come into practice, is effective against both the positive and negative symptoms of schizophrenia (Burris et al. 2002; Kane et al. 2002). At therapeutic doses, aripiprazole occupies 85–95 % of the striatal D_2 receptors without causing the EPS and prolactin elevation commonly associated with such high degrees of D_2 occupancy with antagonists (Gründer et al. 2008; Mamo et al. 2007). With an intrinsic activity of circa 25 %, aripiprazole thus produces levels of D_2 receptor inactivation (i.e., blockade) that ideally fall within the optimal 65–78 % therapeutic window when about 90 % of D_2 receptors are occupied (Mamo et al. 2007). Taken together, studies on the pharmacological action of D_2 antagonists and D_2 partial agonists concur to underline the importance of a fine-tuning of D_2 receptor blockade for achieving optimal antipsychotic benefit and thus further emphasize the central role of this receptor subtype in antipsychotic action.

A few atypical antipsychotics though, namely clozapine and quetiapine, do not fit the conventional window of D_2 receptor blockade suggested for optimal therapeutic response. Clozapine, the prototype of atypical antipsychotic drugs, is

effective in treating patients with refractory schizophrenia (Kane et al. 1988) and, like quetiapine, produces fewer and milder EPS compared to typical antipsychotics and does not induce hyperprolactinemia (Goldstein 1999; Lieberman et al. 1989). Both drugs produce robust antipsychotic effect at less than the conventional 65 % threshold of striatal D_2 receptor blockade (Farde et al. 1989, 1992; Kapur et al. 2000b), suggesting that beyond D_2 receptor blockade in striatum, other receptors or mechanisms also contribute to the therapeutic effect of these drugs. On the other hand, since both clozapine and quetiapine never exceed the 75 % threshold of D2 blockade, they do not give rise to EPS.

2.2.1 Role of Non-D_2 Receptor Blockade

In the search for the involvement of non-DA D_2 receptor mechanisms in antipsychotic action, the D_3 receptor, which has a high homology with the D_2 receptor but displays a preferential distribution in limbic versus motor regions of the dopaminergic systems, has received special attention. In vitro studies have shown that many antipsychotics display comparable affinity for the D_2 and D_3 receptors (Levant 1997; Schotte et al. 1996). However, the relative contribution of D_3 versus D_2 blockade to antipsychotic efficacy has been difficult to establish due to the lack of selective D_3 receptor radioligands and to the partially overlapping distribution of D_2 and D_3 receptors in brain. The development of [^{11}C](+)-PHNO, a preferring-D_3 receptor agonist, has recently permitted to investigate the impact of stable treatment with antipsychotics on D_3 receptors (Graff-Guerrero et al. 2009a). This neuroimaging study, performed in patients with schizophrenia on long-term treatment (>4 weeks) with olanzapine, clozapine, and risperidone, revealed that while antipsychotics induce high levels of D_2 receptor blockade, they do not block D_3 receptors (Graff-Guerrero et al. 2009a). Thus despite displaying D_3 receptor affinity in vitro, these data suggest either that antipsychotics do not bind D_3 receptor in vivo or that they induce a D_3 receptor upregulation on long-term treatment. Subsequent studies performed in rats and comparing D_2 versus D_3 receptor blockade obtained in vitro and ex vivo indicate that, in contrast to what is obtained in vitro, olanzapine, clozapine, risperidone, and haloperidol selectively block D_2 receptors and have only a marginal effect on D_3 receptors ex vivo (McCormick et al. 2011). Altogether, these studies suggest that at clinically relevant doses, the therapeutic effects of antipsychotic are likely not attributable to D_3 receptor blockade. For additional information and discussion, the reader is referred to Gross and Drescher (2012) in the accompanying volume of the Handbook.

The higher affinity of clozapine for D_4 than for D_2 receptors led to the speculation that the superior clinical profile of this drug was due to D_4 receptor blockade (Van Tol et al. 1991). However, several typical antipsychotic drugs, including haloperidol, have similar affinity for D_2 and D_4 receptors (Roth et al. 1995), whereas several atypical drugs, including quetiapine and amisulpride, have very low D_4 affinity, suggesting that D_4 affinity per se does not confer therapeutic efficacy or low EPS liability. Moreover, several clinical trials with D_4 selective

antagonists failed to show antipsychotic efficacy (Bristow et al. 1997; Corrigan et al. 2004; Kramer et al. 1997).

In addition to having D_2-blocking properties, many atypical antipsychotics are also antagonists at the serotonin 5-HT_{2A} receptor and it has been determined that a high 5-HT_{2A}/D_2 affinity ratio is actually the pharmacological feature that best distinguishes atypical from typical antipsychotics (Meltzer et al. 1989). Antagonism at the serotonin 5-HT_{2A} receptor per se does not mediate antipsychotic activity since subtherapeutic doses of atypical drugs such as risperidone and olanzapine induce nearly complete blockade of 5-HT_{2A} receptor in brain, and become therapeutically effective only at doses that cross the conventional 65 % levels of D_2 receptor blockade (Kapur et al. 1999). A balanced inhibition at the D_2 and 5-HT_{2A} receptors is however thought to be important for the reduced side-effect liability and greater ability of atypical versus typical drugs to improve the negative and cognitive symptoms of schizophrenia (Meltzer 2004; Meltzer et al. 2003). This view is however partly challenged by the high incidence of EPS observed with drugs such as chlorpromazine and loxapine despite high levels of 5-HT_{2A} receptor blockade (Kapur et al. 1997; Trichard et al. 1998) and by the lack of EPS observed with amisulpride despite any action on 5-HT_{2A} receptors (Schoemaker et al. 1997; Trichard et al. 1998). Thus, although 5-HT_{2A} may offer advantages against the negative and cognitive symptoms of schizophrenia, low EPS liability is likely unrelated to 5-HT_{2A} receptor blockade.

Preferential Limbic D_2 Receptor Blockade

The underlying mechanism for clozapine's favorable clinical profile, especially with regard to its low EPS liability, has been the focus of intense research. Apart from being attributed to its multireceptor binding profile, especially its binding at the 5-HT_{2A} receptor, it has been suggested that the reduced EPS liability of clozapine, as well as other atypical antipsychotics, is due to a preferential action in limbic and cortical regions (Strange 2001). Indeed, converging evidence from behavioral (Gardner and Seeger 1983; Ljungberg and Ungerstedt 1985; Oakley et al. 1991), electrophysiological (Chiodo and Bunney 1983; White and Wang 1983), and neurochemical (Lane et al. 1988) studies indicate that, in contrast to classical antipsychotic drugs such as haloperidol, clozapine selectively targets the mesolimbic DA system, while leaving the nigrostriatal system relatively unaffected. For instance, while the acute administration of atypical drugs such as clozapine, quetiapine, sertindole, and olanzapine increases the activity of DA neurons in the VTA but not in the SN, haloperidol activates both subpopulations of DA neurons (Goldstein et al. 1993; Hand et al. 1987; Skarsfeldt and Perregaard 1990; Stockton and Rasmussen 1996). As a consequence, atypical antipsychotics preferentially increase DA output in the nucleus accumbens and prefrontal cortex as compared to the striatum whereas the opposite is observed with haloperidol (Hertel 2006; Moghaddam and Bunney 1990; Youngren et al. 1999). Such a preferential modulation of VTA DA neuronal activity likely contributes to the selective development of

depolarization blockade of VTA DA neurons and consequent selective decrease in mesolimbic DA output seen after chronic clozapine treatment, while both the mesolimbic and nigrostriatal DA systems are equipotently affected by chronic haloperidol (Chiodo and Bunney 1983; Goldstein et al. 1993; Lane et al. 1988; Skarsfeldt 1988; White and Wang 1983). Atypical drug's selectivity for limbic, as opposed to striatal, regions is thought to contribute to the lower incidence of EPS as compared to typical drugs. Accordingly, the "limbic selectivity" hypothesis postulates that atypical antipsychotics induce a preferential blockade of limbic and cortical D_2 receptors, which is associated with clinical efficacy, and a relatively lower striatal D_2 receptor blockade, which is associated with a lower incidence of EPS. However, although some imaging studies indicate that atypical drugs such as clozapine, quetiapine, olanzapine, and risperidone block a higher proportion of temporolimbic than striatal D_2 receptors (Bigliani et al. 2000; Bressan et al. 2003; Kessler et al. 2006; Pilowsky et al. 1997; Stephenson et al. 2000; Vernaleken et al. 2011; Xiberas et al. 2001), other studies fail to do so (Agid et al. 2007; Ito et al. 2009; Kessler et al. 2005; Nyberg et al. 2002; Talvik et al. 2001). Atypical drugs have also been shown to produce equipotent D_2 receptor blockade in the ventral striatum (herein the nucleus accumbens is located) and in the dorsal part of the structure (Kessler et al. 2005, 2006), further calling into question the limbic selectivity theory. Moreover, positive symptom reduction in patients treated with risperidone, olanzapine, or aripiprazole appears to be correlated with striatal rather than cortical or other extrastriatal D_2 receptor blockade (Agid et al. 2007; Kegeles et al. 2008), suggesting that the antipsychotic response may be directly mediated through modulation of striatal rather than cortico–limbic DA activity. Clearly, more clinical investigations are needed to determine the exact role of limbic D_2 receptors in the treatment of schizophrenia.

Transient Versus Continuous D_2 Receptor Blockade

Another aspect of D_2 blockade that has been proposed to be central to atypical antipsychotic action is the between-dose kinetic pattern of receptor blockade achieved during clinical dosing (Kapur and Remington 2001b). In vitro work has demonstrated that while drugs such as haloperidol bind with high affinity and display slow dissociation from D_2 receptors, atypical drugs as a group display faster dissociation rates and are only loosely bound to the receptor (Seeman 2002). Such a rapid dissociation is believed to allow D_2 receptors to be released from the drug and to regain responsiveness relatively quickly during the between-dose interval as surges of dopamine can reaccess the receptors. As opposed to typical drugs with slow receptor dissociation, which produce enduring receptor inactivation, atypical antipsychotics would thus only briefly silence D_2 neurotransmission, thereby allowing antipsychotic action with a lower propensity to induce EPS and sustained hyperprolactinemia. As a consequence, and taking into account plasma half-life of the drug and its active metabolites (Tauscher et al. 2002; Tort et al. 2005), drugs with different receptor dissociation properties may produce different kinetics of D_2 blockade. A number of vivo neuroimaging studies concur

to demonstrate that while clinical dosing with haloperidol gives rise to sustained high levels of D_2 receptor blockade (Baron et al. 1989; Nordstrom et al. 1992), D_2 blockade achieved by clinical dosing with quetiapine is only transiently high and declines rapidly after dose intake to reach undetectable levels at 12–14 h postdosing (Catafau et al. 2008; Gefvert et al. 1998; Kapur et al. 2000b; Tauscher-Wisniewski et al. 2002). The demonstration that transiently high D_2 receptor blockade is sufficient for obtaining and maintaining antipsychotic effect, even in drug-naïve schizophrenic patients, thus called into question the presumed necessity of continuous D_2 receptor blockade to control schizophrenia symptoms (Kapur et al. 2000b). In keeping with a precedent pilot study (Remington et al. 2005), a recent double blind study comparing daily with alternate day (also called "extended") antipsychotic dosing in stabilized patients over a 6-month trial period supports this idea (Remington et al. 2011). Patients on extended dosing with risperidone or olanzapine did not show any greater risk of relapse or worsening of positive symptoms as compared to those receiving daily dosing, challenging the common presumption that patients need to receive daily dosing to remain stabilized. It is thus possible that transient D_2 blockade is all that is needed to achieve and/or maintain clinical response and that continuous blockade is unnecessary and may even be detrimental to some aspects of patient outcome. Recent preclinical studies provide further support for this view by documenting the effects of transient versus continuous D_2 receptor blockade in animal models predictive of antipsychotic-like efficacy and side-effect liability. Within-day transient D_2 blockade achieved by transient antipsychotic delivery was found to be more effective than continuous D_2 blockade (Samaha et al. 2007, 2008). Moreover, while continuous D_2 blockade resulted in D_2 receptor upregulation and behavioral tolerance (Ginovart et al. 2009; Samaha et al. 2008) and to an increased risk for the development of vacuous chewing movements (i.e., an animal model for tardive dyskinesia) (Turrone et al. 2003), transient D_2 receptor blockade did not. This finding suggests that between-dose transient D_2 blockade may be sufficient to induce antipsychotic response and may even improve therapeutic efficacy by avoiding the development of compensatory and likely counterproductive D_2 supersensitivity that is obtained under conditions of sustained D_2 blockade. Moreover, as the development of behavioral tolerance and D_2 receptor upregulation is thought to correspond, at least partially, to the emergence of tardive dyskinesia (TD) in patients on long-term antipsychotic treatment (Tarsy and Baldessarini 1977), a transient pattern of D_2 blockade might also have a lower incidence of TD. On the other hand, since D_2 blockade falls quickly after dosing, transiency of D_2 blockade may lead to more rapid relapse on sudden discontinuation or missed doses, especially when using drugs with fastest dissociation kinetics such as clozapine and quetiapine. A central question thus remains that is to determine the optimal between-dose interval producing appropriate D_2 blockade transiency to achieve and/or maintain symptom remission with low risk of relapse. This balance may be a challenge because this between-dose interval is likely to be quite variable amongst patients (given the wide interpatient variability in metabolism), but also amongst antipsychotic drugs (given their variable D_2 dissociation properties and half-life of time residency in plasma).

Pharmacokinetic analysis of D_2 blockade however has good heuristic value for exposing processes underlying the various degrees of atypicality seen among antipsychotics and is thus worth further investigation.

3 Mechanisms Underlying Speed and Onset of Antipsychotic Response

One important measure of antipsychotic effectiveness is the time lag between the initiation of antipsychotic treatment and the onset of therapeutic response. It has long been held that time to onset of clinical response is delayed by 2–3 weeks after initiation of treatment. This delayed onset of antipsychotic response is thought to reflect the induction of late-onset phenomena, such as the cessation of midbrain DA neurons firing, also known as depolarization blockade. Indeed, while acute D_2 receptor blockade increases the firing of mesolimbic DA neurons, this initial activation gradually subsides with successive antipsychotic administration and ultimately leads, after 2–3 weeks of chronic treatment, to a reversible cessation of midbrain DA neuron firing. The delayed onset of antipsychotic response is thus thought to correlate with the delayed inactivation of midbrain DA neurons (Grace et al. 1997). Another hypothesis postulates that long-term drug-induced changes in gene expression, protein synthesis, and synaptic remodeling could also mediate the delayed onset of antipsychotic action (Kuhar and Joyce 2001). Given that steady-state levels of D_2 receptor blockade are achieved within 1–2 days of antipsychotic treatment (Nordstrom et al. 1992; Tauscher et al. 2002), the dissociation between rapid effect of antipsychotics on D_2 receptor blockade and their delayed therapeutic efficacy is thus difficult to reconcile with a central role of D_2 blockade in the mechanism of antipsychotic action. However, recent research does not lend support to the "delayed-onset" hypothesis and growing evidence indicates that response to antipsychotic treatment occurs much earlier than originally thought. In a large and pioneering meta-analysis involving nearly 7,500 patients with schizophrenia treated with typical (haloperidol, chlorpromazine) and atypical (risperidone and olanzapine) antipsychotics, Agid et al. (2003, 2006) found that antipsychotics produce discernible clinical improvement within the very first week of treatment and that improvement in psychosis is actually greater in the first week than in each subsequent 3 weeks of treatment. Such an early onset of symptom response has been found to be true for other antipsychotic drugs, including quetiapine (Pae et al. 2007; Small et al. 2004) and amisulpride (Leucht et al. 2005), and to be a reliable marker of subsequent clinical outcome as early nonresponse to antipsychotics strongly predicts subsequent lack of response to continued treatment with the same medication (Correll et al. 2003; Kinon et al. 2008, 2011; Leucht et al. 2005). Further, it has now been demonstrated that robust clinical improvement of psychosis occurs as early as the first 24 h of treatment (Agid et al. 2008; Kapur et al. 2005) and that early improvement is strongly predictive of eventual improvement (Agid et al. 2008; Kinon et al. 2008). In addition to a consistent finding of early

onset of therapeutic benefit, the degree of D_2 receptor blockade measured as early as 48 h after treatment initiation correlates positively with clinical improvement after 2 weeks of treatment (Catafau et al. 2006), thus suggesting that early response is likely to be directly linked to D_2 blockade. Contrary to the common belief that there is delayed onset of antipsychotic benefit, compelling evidence indicates that effective doses of antipsychotics have nearly immediate effects with symptom improvement occurring within the first week of treatment. The fact that discernible clinical effects occur close in time to the almost immediate neuropharmacological action of antipsychotics suggests that antipsychotic efficacy likely results from direct blockade of the D_2 receptors, rather than a purported indirect and delayed downstream effect on DA neuronal pathways.

4 Linking Dopaminergic Disturbances, Psychology and Pharmacology in Schizophrenia

If we accept a causal relationship between dopaminergic disturbances and psychosis, how can we understand the link between such a biological disturbance and the psychological expression of the disease? In other words, how can an excessive DA function in schizophrenia lead to hallucinations and delusions and not to some other manifestations? Moreover, why do full benefits of antipsychotic treatment take several weeks to months whilst steady levels of D_2 receptor blockade and first effects of treatment can be seen as early as after one day of treatment? A model has been proposed (Kapur 2003; Kapur et al. 2005) that links DA to symptom expression, and its blockade to symptom resolution. Inherent to this model is the central role of mesolimbic DA in the neural processing of motivation and reward-based associative learning (Day et al. 2007). Indeed, DA neurons in the mesolimbic system are activated by reward-predicting stimuli, leading to the release of DA in the terminal fields that regulate behavior. Rather than encoding the hedonic value of reward, activation of DA mesolimbic neurons predicts the likelihood of a reward to occur when a reward-related cue is presented (Schultz 2006). In this context, DA released in response to the reward-predicting cue determines its incentive salience and establishes reward-associated memories such that subsequent exposure to the cue can trigger reward-directed behaviors (Berridge 2007). In the case of schizophrenia, it is hypothesized that excessive mesolimbic DA transmission occurs irrespective of the contextual experience and therefore exaggerated salience is attributed to impertinent stimuli and to internal representations (Kapur 2003; Kapur et al. 2005). In support of this hypothesis, increasing evidence obtained in schizophrenia patients indicates an abnormally high physiological response of the ventral striatum to non-reinforced stimuli during reward conditioning, suggesting an abnormal ability to differentiate neutral from motivationally salient stimuli (Diaconescu et al. 2011; Jensen et al. 2008; Murray et al. 2008). Misattribution of motivational salience to irrelevant events translates into distorted thoughts and false perceptions of events that contribute to the formation of delusion as a way for the

patient to provide a rational explanation to abnormal internal and external events and give sense to his/her surrounding world. By blocking mesolimbic DA transmission, antipsychotics would not resolve delusional beliefs per se but would rather dampen aberrant salience such that new experiencing can progressively change the patient's cognitive and emotional experience. Resolution of delusions thus follows a slower course than the immediate antipsychotic-induced dampening of salience because it requires cognitive and psychological work from the patient to overcome the false beliefs. Moreover, since antipsychotics also dampen normal incentive salience, they may contribute to the depressed mood, increased anhedonia, and amotivation associated with treatment, thus explaining some of the undesirable effects of antipsychotics.

5 Conclusion and Future Directions

The last 50 years of research have provided unquestionable evidence for a central role of D_2 receptor blockade in the mechanism of antipsychotic action. The demonstration that therapeutic response is a function of the degree of D_2 blockade and that adequately high levels of D_2 blockade are needed to achieve therapeutic efficacy has constituted key discoveries for our understanding of how antipsychotics work. The complex pharmacology, the different DAergic properties, and differential clinical profiles of atypical versus typical antipsychotic agents have moreover provided useful clues with regard to uncovering the potential mechanisms underlying lower EPS liability. While action at the D_2 receptor remains indispensable for controlling the positive symptoms, sustained D_2 blockade may not be necessary for maintaining antipsychotic response and extended antipsychotic dosing leading to transiently high D_2 blockade may represent an effective strategy to circumvent undesirable side effects associated with continuous dosing. Other key modulators of antipsychotic activity include activity at other receptors, especially at the 5-HT_2 receptor, and are probably required for ameliorating the negative and cognitive symptom domains for which D_2 blockade appears ineffective. Yet, and despite continuous research in the field, the fundamental principle has remained unchanged—D_2 blockade remains necessary and sufficient for the antipsychotic response.

Nevertheless, currently available antipsychotics are not ideal since even atypical drugs, which show benefits in terms of EPS, have an increased risk of weight gain and metabolic disturbances. Additional progress is thus still needed and the search for other pharmacological strategies to treat schizophrenia continues. New treatment approaches to tackle schizophrenia could aim at more directly interrupting the pathophysiological mechanism leading to psychosis rather than just blocking its downstream effect. Indeed, whilst most current antipsychotics are D_2 blockers, no conclusive D_2 abnormalities have yet been identified in schizophrenia and converging evidence indicates that the definitive abnormality contributing to abnormally high DA functioning largely resides presynaptically. Rather than just blocking the downstream effects of inappropriately released DA, new therapeutic strategies

could be directed on upstream factors that control the presynaptic release of DA. One such strategy is currently focused on the use of a glutamate receptor agonist and has provided promising results in patients (Patil et al. 2007), and may thus offer a future alternative to complement or replace the use of D_2 blockers. The pathophysiological mechanisms underpinning a presynaptic DAergic hyperfunction in schizophrenia are however still poorly understood, which limits the rational development of new therapeutics. A better elucidation of those mechanisms will be the challenge of future research on schizophrenia and may provide a rational basis for new pharmacotherapies. The next decade of research will tell whether the DA system has delivered all it can for the treatment of schizophrenia—or whether there are further opportunities to harness it for the benefit of our patients.

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