Dopamine and the Biology and Course of Treatment Resistance

3

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3.1 Introduction

A key question faced by any clinician is why some patients respond to standard treatments, whilst others don't. Understanding this is likely to be a prerequisite to developing better treatments for refractory patients. It will also help the development of biomarkers to identify these patients early so they can be fast-tracked to appropriate treatments, avoiding the current clinical merry-go-round of empirical trials with different antipsychotics. This chapter first considers the pathophysiology of schizophrenia and treatment response, focusing on the dopamine (DA) system as this is central to the mode of action of current drugs. It then considers the course of refractory schizophrenia and whether treatment resistance is present from illness onset or evolves during the course of illness. Finally, it considers whether we can answer the question posed at the start of this chapter.

3.2 The Role of DA in the Neurobiology of Schizophrenia

Whilst the neurobiology of schizophrenia is complex, it has become clear that dopaminergic alterations play a central role in the pathophysiology of the disorder and its treatment (Abi-Dargham 2004; Howes and Kapur 2009). The first evidence of this came from in vitro findings indicating that antipsychotics work by blocking DA D2/3 receptors and from psychopharmacological studies showing that drugs

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that activate the DA system such as amphetamine can induce psychotic symptoms (Abi-Dargham 2004; Howes et al. 2009a; Berman et al. 2009; Curran et al. 2004). Subsequent post-mortem studies have also identified elevations in DA levels and DA D2/3 receptor densities in patients with schizophrenia (Bird et al. 1979; Cross et al. 1978; Zakzanis and Hansen 1998). However, as the post-mortem findings were predominantly from patients who had been treated for schizophrenia for many years, it was not clear whether the DA abnormalities were primary or secondary to treatment or late stage sequelae of the disorder. Subsequent molecular imaging studies were able to clarify this by studying untreated patients at onset or relapse of the disorder. A recent meta-analysis of the now more than 50 molecular imaging studies of the DA system in schizophrenia has identified three important findings to come out of this work. First, alterations in D2/3 receptor availability are inconsistent and small at most (Howes et al. 2012). Second, DA transporter availability is unaltered (Howes et al. 2012; Chen et al. 2013). Third, there is robust evidence for presynaptic DA alterations, specifically elevated DA synthesis capacity (Table 3.1), increased DA release, and elevated baseline synaptic DA levels in schizophrenia. The effect sizes for these alterations are large (Cohen's $d > 0.8$) (Howes et al. 2012), much larger than that for ventricular enlargement, for example. In short, this pinpoints presynaptic dysregulation as the major locus of DA dysfunction in the disorder (Howes et al. 2009a, 2011a, b; Lyon et al. 2011). Moreover, it does not seem to be a non-specific mark of psychiatric illness—for example, presynaptic DA function is unaltered or reduced in people with depression, bulimia, addictions, anxiety disorders and non-psychotic bipolar disorder [see review (Howes et al. 2007)], although it may be elevated in people with psychosis linked to temporal lobe epilepsy (Reith et al. 1994) and people with schizotypal personality disorder, who have psychotic-like symptoms (amongst other schizophrenic traits) (Abi-Dargham et al. 2004) and increased DA synthesis capacity (Howes et al. 2011a). Molecular imaging studies that index DA release following amphetamine in patients with schizophrenia indicate that greater release is associated with greater induction of psychotic symptoms (Laruelle et al. 1999). This is also the case when DA levels are depleted with inhibitors of DA synthesis: greater depletion following inhibition of DA synthesis is directly associated with greater reduction in psychotic symptoms (Abi-Dargham et al. 2000). Moreover, DA release was greater in patients who are acutely psychotic than in remitted patients (Laruelle et al. 1999). Taken together these findings thus link presynaptic DA alterations to the expression of symptoms in schizophrenia.

However, whilst these findings implicated DA in the pathophysiology of schizophrenia, it was still unclear if DA abnormalities were leading to the disorder or were developing secondary to the onset of the illness. To address it was necessary to study the development of the first episode of illness. Schizophrenia is typically preceded by a prodromal phase of subclinical psychotic symptoms and subtle functional changes. People who present with these features indicating a high clinical risk of developing schizophrenia in the next year or so show a large effect size increase in DA synthesis capacity, similar to that seen in schizophrenia although not as large (Howes et al. 2009b; Egerton et al. 2013). However, not all

Table 3.1 The PET imaging studies of dopamine synthesis capacity in schizophrenia

Study	Patients (*N*)	Controls (*N*)	Age	Illness stage	Radiotracer	Medication status	Effect size
Reith et al. (1994)	5	13	38	Chronic	[^{18}F]-DOPA	4 MN 1 MF	1.52
Hietala et al. (1995)	7	8	26	FEP	[^{18}F]-DOPA	All MF	0.9
Dao-Castellana et al. (1997)	6	7	26	Chronic	[^{18}F]-DOPA	2 MN 4 MF	0.35
Hietala et al. (1999)	10	13	30	FEP	[^{18}F]-DOPA	All MF	1.02
Lindstrom et al. (1999)	12	10	31	FEP/ Chronic	[^{11}C]-DOPA	10 MN 2 MF	1.01
Elkashef et al. (2000)	19	13	36	Chronic	[^{18}F]-DOPA	9 MF 10 M	−0.13
Meyer-Lindenberg et al. (2002)	6	6	35	Chronic	[^{18}F]-DOPA	All MF	1.82
McGowan et al. (2004)	16	12	38	Chronic	[^{18}F]-DOPA	All M	1.55
Kumakura et al. (2007)	8	15	37	Chronic	[^{18}F]-DOPA	3 MN 5 MF	0.10
Nozaki et al. (2009)	18	20	36	FEP/ Chronic	[^{11}C]-DOPA	14 MN 4 MF	0.13
Howes et al. (2009a, b)	7	12	36	FEP	[^{18}F]-DOPA	3 MN 4 MF	1.18
Shotbolt et al. (2011)	7	10	43	Chronic	[^{18}F]-DOPA	All M	0.07
Demjaha et al. (2012)	12	12	44	Chronic-Responders	[^{18}F]-DOPA	All M	1.12

Abbreviations: *FEP* first episode psychosis, *MN* medication naïve, *MF* medication free

clinically high risk individuals are truly in the prodrome to schizophrenia. Follow-up of these individuals shows that elevated DA synthesis capacity is specific to those who go on to develop schizophrenia/similar disorder (Howes et al. 2011a). Moreover, DA synthesis capacity is directly associated with the severity of subclinical symptoms in these individuals but not in those who do not go on to develop a psychotic disorder (Howes et al. 2011a). These individuals show functional recovery, but many continue to experience subclinical psychotic symptoms. In this respect they are similar to people in the general population who experience subclinical psychotic symptoms (Hanssen et al. 2005). A study of such people who had experienced subclinical psychotic symptoms for many years without impairment or distress and without developing a psychotic disorder also found no evidence of DA elevation (Howes et al. 2013). Another group in whom subclinical psychotic symptoms and other schizophrenic traits are seen is relatives of people with schizophrenia, but here the findings are contradictory (Huttunen et al. 2008; Shotbolt et al. 2011).

Furthermore, a longitudinal study where patients were scanned in the prodrome and then again after they developed acute psychosis found an increase in DA synthesis capacity during the progression from the prodrome to the first psychotic episode, whilst DA synthesis capacity did not change in those "at risk" individuals who did not go on to develop psychosis (Howes et al. 2011b).

These findings indicate a link between greater DA dysfunction and the development of more severe psychotic symptoms and suggest that the DA dysfunction is dynamic, increasing with the worsening of the disorder. However, whilst DA dysfunction appears most marked in acute psychosis, it is not confined to schizophrenia per se, but is also seen in people with other psychotic disorders and people with subclinical psychotic symptoms and schizophrenic traits.

3.3 Drugs, Receptors and Treatment Response

Whilst antipsychotic drugs block D2 DA receptors, they also act at a number of other brain receptors, in particular other DA receptors and serotoninergic, histaminergic, norepinephrinergic and cholinergic receptors. This complexity meant it was initially far from clear where they were acting therapeutically in the brain. The studies in the 1970s showing the relationship between the affinity of antipsychotic drugs for D2 receptors and their clinical potency first made a clear link between D2 receptors and therapeutic outcome (Seeman and Lee 1975). However, these studies were in vitro, a very different system to a brain, not least because brains are protected by a barrier that effectively excludes many drugs. Molecular imaging studies since then have provided in vivo evidence to support the in vitro findings, first by showing that the drugs cross the blood–brain barrier in humans and secondly that they block D2/3 striatal receptors in vivo at doses in the usual therapeutic ranges (Howes et al. 2009a). This is also true of the newer drugs so far studied [e.g., (Kapur et al. 1999; Kegeles et al. 2008)]. Subsequent molecular imaging studies have gone on to characterise a number of aspects of the relationship between DA receptor occupancy and clinical response.

A key finding is that the relationship between antipsychotic D2 receptor occupancy and clinical response appears to be non-linear: there is little clinical response seen when occupancy is less than 50 % and little additional benefit for occupancy levels much greater than 80 % (Kapur et al. 2000). Thus, there appears to be a therapeutic window. Figure 3.1 illustrates this, showing there is a minimum level of D2 occupancy required for clinical response to antipsychotic drugs and a level above which there is little further advantage but increased risk of side effects. A study in first episode patients tested this using [11C]raclopride PET scans to measure D2 receptor occupancy after patients had received 2 weeks of antipsychotic treatment.(Kapur et al. 2000) Subsequent clinical response was assessed using the global clinical impression of how much the patients had improved. Responders were those who were much or very much improved, whilst non-responders were defined as those with little or no response. The study supported the idea there is a therapeutic window, finding that antipsychotic D2

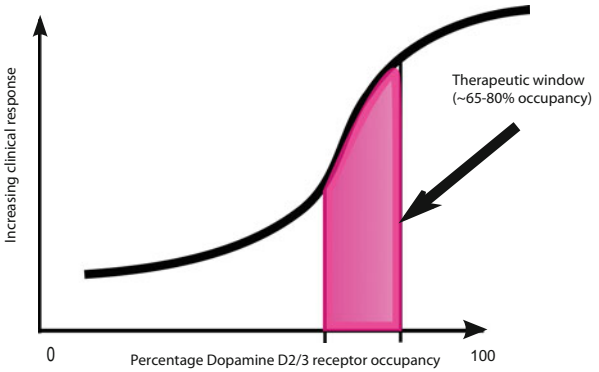

Fig. 3.1 The relationship between clinical response and dopamine receptor occupancy

occupancy of 65 % best distinguished responders from non-responders: 80 % of responders showed >65 % receptor occupancy, whilst 67 % of the non-responders had occupancy below the 65 % threshold. They also found that occupancy levels much above 80 % were associated with an increased risk of side effects. The notion of a therapeutic window of D2 occupancy for clinical response has subsequently been confirmed by a meta-analysis of imaging studies for a range of the most commonly used antipsychotics.(Yilmaz et al. 2012) However, it is important to note that in the first episode study, about one-third of the non-responders showed occupancy levels above the threshold.(Kapur et al. 2000) Thus, whilst some non-response may be due to inadequate receptor occupancy, there is still a proportion of patients who show inadequate response despite good D2 occupancy.

The role of other receptors has also been examined in vivo. The observation that clozapine, the only antipsychotic licensed for refractory schizophrenia, showed high levels of serotonin 2A receptor antagonism at clinical doses underpinned efforts to develop antipsychotic drugs that reproduced this aspect of clozapine's pharmacology without its tolerability issues. In the 1990s a number of second generation antipsychotics that showed high serotonin 2A receptor antagonism came to market. In vivo studies have subsequently investigated serotonin 2A occupancy in healthy volunteers and patients at clinical doses of these drugs. These studies have found that high levels of serotonin 2A occupancy is already apparent at low doses of these drugs, for example, risperidone at 2 mg and olanzapine at 5 mg (both generally sub-therapeutic doses) show serotonin 2A occupancy of >80 % (Kapur et al. 1999). Furthermore, a study that compared cortical serotonin 2A occupancy in patients randomised to either olanzapine or clozapine found that serotonin 2A occupancy was not significantly different between the patients on olanzapine (mean dose ~18 mg/day) and clozapine (mean dose ~325 mg/day) but, whilst both groups of patients improved with treatment, the patients on clozapine showed a significantly greater improvement in positive symptoms, suggesting that serotonin 2A occupancy alone does not explain clozapine's superiority (Moresco et al. 2004). Furthermore, even for an antipsychotic such as risperidone that shows high levels of serotonin 2A antagonism, there is a striking relationship between D2 occupancy and clinical response (r values

>0.75) (Catafau et al. 2006). It is also worth noting that chlorpromazine at higher doses (500–700 mg/day) shows high levels of serotonin 2A occupancy, similar to levels seen with clozapine (Trichard et al. 1998). In contrast, amisulpride, a second generation antipsychotic, shows almost no serotonin 2A receptor occupancy at clinical doses (Trichard et al. 1998). As amisulpride is as effective as drugs with high serotonin 2A occupancy, such as risperidone and olanzapine, this is further evidence that serotonin 2A occupancy does not explain antipsychotic efficacy. Other studies have investigated D1 receptor occupancy and clinical response. Here, again there are large differences between drugs at clinically relevant doses, suggesting that D1 occupancy is not a requirement for clinical response (Reimold et al. 2007).

In summary, D2 occupancy is needed for therapeutic response in general, and low levels of D2 occupancy are linked to inadequate response. Thus, in some patients increasing the dose will help. However, it is also clear that some patients do not respond despite high levels of DA D2 receptor occupancy. Thus, D2 receptor occupancy is not sufficient to guarantee response in a proportion of patients. This raises the question what is different about the biology of the DA system in refractory patients.

3.4 The Presynaptic DA System and Treatment Response

Given that presynaptic DA dysfunction is the major locus of dopaminergic abnormality in the disorder, this is the obvious contender for a difference in the DA system between responders and refractory patients. The first studies to investigate this were studies that measured levels of DA metabolites in plasma or cerebrospinal fluid in relation to antipsychotic response. The major DA metabolite examined is homovanillic acid (HVA). Higher baseline DA metabolite levels are generally associated with good subsequent response to antipsychotic treatment, whilst lower DA metabolite levels are associated with poor response (Yoshimura et al. 2003; Mazure et al. 1991; Pickar et al. 1984). Furthermore, there is some evidence that there is a bimodal distribution of HVA levels amongst patients with schizophrenia that is linked to subsequent response to antipsychotics (Ottong and Garver 1997; Bowers 1991). The first peak is higher than that seen in controls, and is seen in patients who respond to antipsychotics, whereas the second peak, at a similar level to control levels, is associated with non-response. A limitation of the plasma HVA measures used in many studies is that they are influenced by peripheral as well as central DA metabolism. Nevertheless, the same pattern of high HVA levels in responders and levels in non-responders is seen when cerebrospinal fluid is used (Pickar et al. 1992). Most of these studies examined non-response to one antipsychotic rather than resistance to multiple antipsychotics, but the same pattern is seen in studies of patients who met treatment resistance criteria (Pickar et al. 1992; Risch and Lewine 1993; Lieberman et al. 1994).

Of course, whilst elevated HVA levels in responders are consistent with the notion that DA levels are elevated in responders, there are alternative

explanations—they could reflect increased metabolism of DA, or reduced metabolism of homovanillic acid, for example—that could account for the differences between responders and non-responders.

Baseline synaptic DA levels in the striatum, indexed using a DA depletion paradigm, have been measured in relation to treatment response (Abi-Dargham et al. 2000). In this study Abi-Dargham and colleagues found that higher synaptic DA levels were associated with a better response to antipsychotic treatment. However, this study did not determine if the patients who showed a poor response were treatment resistant. A more recent imaging study examined DA synthesis capacity in patients who met rigorous treatment resistance criteria and compared them to patients who had shown a good response to antipsychotics, defined as meeting standardised criteria for remission. Interestingly, DA synthesis capacity in resistant patients was not significantly different from that in matched controls (Demjaha et al. 2012). Furthermore, a proportion of these patients then went on to have magnetic resonance spectroscopy to index glutamate levels in the anterior cingulated cortex. Here, the pattern was the opposite: the treatment-resistant patients showed elevated glutamate indices, whereas the responders showed lower glutamate levels that were not significantly different to those seen in matched controls (Demjaha et al. 2013a). These findings thus suggest that there is a double dissociation in DA and glutamate function between responders and resistant patients.

3.5 The Onset and Course of Treatment Refractory Schizophrenia

One issue that bedevils the interpretation of research into the biology of treatment resistance is that most of the studies are in chronic patients. Indeed, by definition patients will have had to have at least two treatment courses and so will have been ill for some time. It is thus not clear whether differences observed in treatment-resistant patients were present from illness onset or developed later. This links to the on-going debate in the field as to whether treatment resistance in schizophrenia evolves over time, perhaps as a consequence of untreated psychosis, or is manifest at the onset of illness. In line with a first notion, Wyatt (1991) reviewed the evidence derived from 22 studies of predominantly first episode patients that examined the effect of medication on the natural course of schizophrenia. Based on this he suggested that early psychopharmacological intervention improves outcome and prognosis, and proposed that a neurodegenerative process may be inherent to psychosis and thus unfavourably affect the clinical course in those who are non-compliant and subjected to multiple relapses. In a subsequent review of clinical studies, he synthesised the evidence showing that patients who received antipsychotic treatment early in the course of illness, specifically during their first or second hospitalisation, had a much better outcome than patients who did not receive any treatment (Wyatt 1995). This gave support to the "neurodegeneration hypothesis" suggesting that psychotic episodes have a neurotoxic effect on the

brain. However, numerous MRI studies have subsequently addressed this question and, whilst it is clear that brain changes do evolve in some patients, it remains possible that this is due to the effect of antipsychotic treatments (Zipursky et al. 2012).

Another possibility is that a proportion of patients become less responsive to pharmacological treatment as the illness progresses. Kolakowska et al. (1985) examined retrospective accounts of medicated patients 2–20 years after their first presentation to investigate this. However, the authors found that majority of 40 poor responders in their sample were unresponsive throughout the illness and thus concluded that treatment response is related to the "type" and not the "stage" of illness. The retrospective design of this study could have led to a measurement error leading to information bias. Still, as the authors rightly suggest, the bias would be towards "over-estimation" of remission particularly in cases were associated behavioural disturbance was not recorded. In addition, two other longitudinal studies have similarly observed that a refractory illness course is apparent in early stages of illness in a proportion of patients (Bleuler 1978; Huber et al. 1975). More recently, a large follow-up study of first episode patients that specifically examined the development of treatment resistance over the 10-year follow-up found that over 80 % of treatment-resistant patients were persistently resistant from the initiation of antipsychotic treatment (Demjaha et al. 2013b). Moreover, about 20 % of first episode psychosis patients appear to be resistant to medication at a very early stage of their illness, and at the time of initiation of treatment,(Agid et al. 2011; Robinson et al. 1999; MacMillan et al. 1986; Lieberman et al. 1996) which cannot be explained by the effects of medication, neurochemical sensitisation or neurodegeneration.

Thus, the longitudinal studies suggest that both models are right: a proportion, the clear majority, of treatment-resistant patients are resistant from onset, but there is a proportion who develop it later in their illness. Given that the clear majority of treatment-resistant patients are resistant from onset, the studies of treatment-resistant patients are likely to largely reflect the biology of treatment resistance from illness onset.

What, then, could underlie the development of treatment resistance in those patients who develop it during the course of their illness? There is evidence from animal studies that chronic treatment with DA blocking antipsychotics induces DA D2 receptor up-regulation, which could reduce the efficacy of antipsychotic treatment and lead to breakthrough DA supersensitivity. (Samaha et al. 2007; Ginovart et al. 2008) This implies that the development of DA supersensitivity may predispose some patients to becoming resistant following repeated and long-term exposure to antipsychotic treatment.

It should be noted that there is a third group of treatment-resistant patients who achieve spontaneous remission or start responding to treatment later in life (Meltzer 1997). Observations that older schizophrenic patients require much lower antipsychotic doses than their younger counterparts (Fenton and McGlashan 1987) suggest that the development of treatment responsiveness could be related to age-related reductions in dopaminergic transmission (Dreher et al. 2008; Reeves et al. 2002).

However, whilst this would explain the resolution of treatment resistance due to breakthrough DA supersensitivity, it would not account for resolution of resistance in patients who have been treatment resistant from onset.

Conclusion

The question raised at the beginning of the chapter was what underlies why some patients respond to antipsychotic treatment and others do not. Research over recent decades allows us to go some way to answer this. It is clear that presynaptic dopamine dysregulation is a consistent finding in schizophrenia and linked to the onset of psychosis. It would take a lot of new evidence to overturn this finding. This indicates that by blocking dopamine receptors, antipsychotic drugs are acting on the right system. It is also clear that adequate dopamine receptor blockade is central to the mode of action of all first-line (non-clozapine) antipsychotics, with D2 receptor occupancy greater than a threshold of 65 % or so linked to antipsychotic efficacy. Nevertheless, some patients do not respond despite adequate D2 blockade. The studies of dopamine metabolites in the 1990s and the more recent molecular imaging studies indicate that non-responders do not show the same dopamine abnormality seen in the majority of patients. This would explain why they do not respond to dopamine blocking drugs. Moreover, recent results suggest that treatment-resistant patients instead show altered glutamate function. However, this finding requires further testing, and there are questions that remain outstanding, not least whether these biological differences exist at illness onset or whether they develop during the course of the illness. The fact that treatment resistance is present early in the illness suggests that they are likely to be present at illness onset for the majority of treatment-resistant patients, but longitudinal imaging studies are required to definitively determine this.

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