Journal of Psychopharmacology

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>> Version of Record - Jun 16, 2010

OnlineFirst Version of Record - Nov 25, 2009

What is This?

The biological basis of antipsychotic response in schizophrenia

James M. Stone, Marie Raffin, Paul Morrison and Philip K. McGuire

Abstract
Schizophrenia is a severe mental illness affecting approximately 1% of the population worldwide. Antipsychotic drugs are effective in symptom control in up to two-thirds of patients, but in at least one-third of patients the response is poor. The reason for this is not clear, but one possibility is that good and poor responders have different neurochemical pathologies, and may therefore benefit from different treatment approaches. In this selective review we summarise research findings investigating the biological differences between patients with schizophrenia who show a good or a poor response to treatment with antipsychotic drugs.

Introduction

Schizophrenia affects approximately 1% of the population, with an age of onset in the late teens or early twenties. The disorder usually follows a chronic relapsing–remitting course, and severely limits the individual's ability to work and to integrate into society. Positive (hallucinations, delusions, speech disturbance) and negative psychotic symptoms (social withdrawal, apathy, loss of emotional response) are accompanied by marked impairments in social and cognitive function. The overall cost to society of caring for people with schizophrenia is enormous, being one of the most expensive disorders across the adult lifespan (Bartels et al., 2003).

The discovery of chlorpromazine in the 1950s heralded a breakthrough in the treatment of schizophrenia. It was the first drug to have a marked effect in reducing psychotic symptoms, and its discovery opened the gates for a flurry of other antipsychotic drugs with similar efficacy. Experimental research revealed that the primary mechanism of action of these drugs was through dopamine D2 receptor blockade (Creese et al., 1976; Seeman et al., 1975).

Subsequent clinical experience with these drugs indicated that approximately one-third of patients failed to respond to antipsychotic treatment. It was initially hypothesised that non-responders might be taking sub-therapeutic doses, which led to the relatively common use of 'mega dose' antipsychotic therapy in the 1980s (Pantelis and Barnes, 1996). The development of single photon emission computed tomography (SPECT) imaging allowed striatal D2 receptor occupancy to be assessed in living subjects. It emerged that patients who failed to respond to antipsychotic drugs still had very high (around 90%) striatal D2 receptor occupancy (Pilowsky et al., 1993), suggesting that non-responders to antipsychotic drugs might represent a subgroup in which D2 receptor blockade was not associated with clinical benefit.

Clozapine is a unique antipsychotic drug, in that a proportion of patients with schizophrenia who do not improve on any other antipsychotic drug may still respond to clozapine (Kane et al., 1988). Furthermore, it has a much lower propensity to induce extrapyramidal side effects (EPSEs) than first-generation antipsychotic drugs (FGA). Work using SPECT revealed that despite its enhanced efficacy in some non-responders, clozapine treatment resulted in only modest striatal D2 receptor occupancy at clinically effective doses (Farde and Nordstrom, 1992; Pilowsky et al., 1992). This suggested that a different or additional mechanism of action was responsible for clozapine's superior efficacy and lower EPSE potential.

Following this finding, there were considerable efforts by pharmaceutical companies to develop drugs mimicking clozapine's profile. A number of second-generation antipsychotic drugs (SGAs) were developed (risperidone, amisulpride, olanzapine, sertindole). These all had a lower propensity to EPSEs and were associated with lower striatal D2 receptor occupancy (Stone et al., 2008a), yet none proved as clinically effective as clozapine. Recent studies have now shown that, clozapine aside, none of the other SGAs differ from FGAs in terms of efficacy (Lewis and Lieberman, 2008).

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Thus, patients with schizophrenia can be divided into three groups according to their response to antipsychotic drugs: (1) those who respond to non-clozapine antipsychotic drugs, (2) those who respond only to clozapine and (3) those who do not respond to any antipsychotic drug (including clozapine). A parsimonious explanation of this difference in response is that each subgroup has a distinct neurochemical profile. Understanding the neurochemical differences between these subgroups of may therefore inform the development of drugs for patients with treatment refractory schizophrenia.

In this review we summarise the literature examining biological differences between responders and non-responders to antipsychotics in an attempt to clarify what might underlie non-response. As we are primarily interested in differences that might be amenable to pharmacotherapy, we consider only studies with direct biological measures: genetic, biochemical and neuroimaging studies. Finally, we consider theoretical models for antipsychotic non-response and suggest potential new avenues for research.

It should be noted that this approach is not without its difficulties: definitions of treatment response and treatment resistance differ, sometimes significantly, between different studies. Furthermore, there are differences in methodology and in patient populations studied. Many papers simply report associations with non-response during drug treatment, which, nonetheless, have the potential to shed light on potential mechanisms underlying good and poor response to antipsychotic treatments, while others attempt to identify predictors of response, which, if robust, would have additional utility in clinical tailoring of medication to individual patients. We shall endeavour to highlight these potential sources of discrepancy in findings as they are discussed.

Genetic associations with treatment response

Over the last 40 years, family, twin and adoption studies have clearly established that schizophrenia has a major genetic component. Transmission patterns within families indicate the involvement of multiple susceptibility genes, with each individual genetic variant having a relatively small effect size (Allan et al., 2008). Currently it is thought that schizophrenia results from distinct gene × gene (epistatic) and/or gene × environmental interactions (although appreciation of epigenetic mechanisms may, in turn, necessitate revisions to this simple interactive model). Many different genetic variants have been implicated as risk factors for schizophrenia and it is often assumed that they converge onto a common neurochemical signalling system. However, the category of schizophrenia may subsume a number of different disorders with distinct genetic and neurochemical underpinnings, which, nevertheless, are associated with similar psychiatric symptoms and signs. The latter is of particular interest when considering non-response to antipsychotic medication. It is feasible that patients who fail to respond to D2 receptor blockade may differ, at a biological level, from those who make a good response. Interest in the field of pharmacogenetics in schizophrenia has rapidly flourished, with many groups investigating genetic associations with drug side effects as well as with treatment response (Arranz and de Leon,

2007). In this section we consider the evidence for genetic differences between good and poor responders to antipsychotic drug treatment. The experimental strategy in the literature to date has been to examine associations between markers in candidate genes (either metabolic or neurochemical) and treatment response. Here we focus on neurotransmitter related genes.

Dopamine receptors

There has been considerable interest in examining whether treatment response is associated with genetic variation in components of the dopamine system. The first gene to be explored was DRD2, encoding the D2 receptor. Several studies showed that improved positive symptoms (Schafer et al., 2001; Suzuki et al., 2000) as well as increased motor side effects (Alenius et al., 2008; Guzey et al., 2007; Zai et al., 2007) during treatment with antipsychotics were associated with genotype at the Taq1A locus. However, many studies have failed to replicate these findings (Kaiser et al., 2002; Wu et al., 2005, 2006; Xing et al., 2007), whilst Hwang and colleagues found that genotype at Taq1A was predictive of response to clozapine in an African-American but not in a Caucasian sample (Hwang et al., 2005). The Taq1A locus, 10 kB downstream of DRD2, has now been shown to be within the coding region of a neighbouring gene termed ankyrin repeat and kinase domain containing 1 (ANKK1) making interpretation of findings in terms of dopamine neurochemistry particularly challenging (Neville et al., 2004). Furthermore, although several studies have reported an association between a functional polymorphism (-141C Ins/Del) in the DRD2 promoter and treatment response (Suzuki et al., 2001; Wu et al., 2005), others have not (Arranz et al., 1998; Hwang et al., 2005; Ohara et al., 1998; Xing et al., 2007). Thus, evidence for an association between polymorphisms of the dopamine D2 receptor and antipsychotic response is not strong.

Many antipsychotic drugs act at other D2-like receptors, with several drugs having modest affinity for the D3 subtype, and clozapine acting as an antagonist at D4 receptors. There have been reports of an association between a functional polymorphism in DRD3 (Ser9Gly) and treatment response (Adams et al., 2008; Lane et al., 2005; Reynolds et al., 2005; Shaikh et al., 1996; Scharfetter et al., 1999; Szekeres et al., 2004). However, among these positive reports there are inconsistencies as to which allele is associated with a better treatment response. In addition, several studies have found that the DRD3 (Ser9Gly) genotype did not predict clinical response to risperidone (Kim et al., 2008), clozapine (Barlas et al., 2008; Malhotra et al., 1998), or FGAs (Cordeiro et al., 2006; Fathalli et al., 2008).

Regarding the D4 receptor, a 48-bp repeat polymorphism (48-bp VNTR) in DRD4 has been associated with clinical response to antipsychotic drugs (Cohen et al., 1999; Hwu et al., 1998), including clozapine (Zhao et al., 2005). However, in a study of over 600 psychotic patients, genotype at the 48-bp VNTR did not predict antipsychotic response (Kaiser et al., 2000). Furthermore, the majority of studies have found no association between DRD4 genotype and response to risperidone (Zalsman et al., 2003) or clozapine

(Kohn et al., 1997; Rao et al., 1994; Rietschel et al., 1996; Shaikh et al., 1995).

Although currently available antipsychotic drugs do not have direct action at D1 receptors, there has been increasing interest in the role that these receptors play in the pathophysiology of schizophrenia (Abi-Dargham and Moore, 2003). It has been suggested that the disorder may involve reduced dopamine stimulation of cortical D1 receptors, since there is thought to be a reciprocal relationship between cortical and striatal dopamine release (Pycock et al., 1980). Reduced cortical dopamine release might conceivably be related to negative symptoms and cognitive deficits (Abi-Dargham and Moore, 2003), and some researchers have hypothesised that the enhanced action of clozapine might occur through modulation of this pathway. One group found a superior response to clozapine with the 2,2 D1 receptor allele and aggravation of symptoms with the 1,2 allele (Potkin et al., 2003), but another group failed to replicate this finding (Hwang et al., 2007).

COMT

The main route for dopamine clearance in the cerebral cortex is metabolism by the enzyme Catechol-O-methyltransferase (COMT). A functional polymorphism at Val108/158Met which influences the rate of dopamine breakdown by COMT has been associated with working memory performance in some (but not all) studies (Tunbridge et al., 2006). Several groups have investigated the Val108/158Met polymorphism as a predictor of treatment response. Reports that the Met allele was associated with a poorer response to antipsychotic drugs (Illi et al., 2003; Inada et al., 2003) were not replicated in similar studies (Illi et al., 2007; Nolan et al. 2006), whilst another found that the Val allele predicted a poorer response (Molero et al., 2007). It has also been reported that the Met allele predicted improved negative symptoms in patients treated with olanzapine (Bertolino et al., 2007). Two small-scale, but intriguing studies found an association between the Met allele and improved working memory performance following treatment with olanzapine (Bertolino et al., 2004) and other SGAs (Weickert et al., 2004). In a larger study of patients treated with clozapine, there were associations between the Met allele and improvements in attention and verbal fluency, but in contrast to the findings of Bertolino et al. and Weickert et al., the Met allele was predictive of poorer working memory performance following treatment (Woodward et al., 2007). It should be borne in mind that as COMT Val108/158Met variants are very common, it would be unlikely that they would be the sole predictor of treatment response, but this does not preclude the possibility that they may interact with other genetic polymorphisms in determining response to antipsychotic treatment in patients with schizophrenia.

Serotonin receptors

Given that many SGAs have actions at serotonin (5HT) receptors, there has been considerable interest in the relationship between serotonin receptor polymorphisms and response to antipsychotic treatment. Several different 5HT2A receptor polymorphisms have been studied. One of the first to be examined was the 102T/C polymorphism, with a study showing a relationship with clozapine response (Arranz et al., 1995). Two further studies have found a relationship with risperidone response (Kim et al., 2008; Lane et al., 2002). In contrast, six studies of the 102T/C polymorphism found no relationship with treatment response (Alenius et al., 2007; Lin et al., 1999; Malhotra et al., 1996a; Masellis et al., 1995, 1998; Nothen et al., 1995). Other polymorphisms such as 19G/T and 12A/T (Birkett et al., 2000) and 452Tyr (Arranz et al., 1996; Malhotra et al., 1996a; Nothen et al., 1995) were not strongly associated with treatment response.

A few groups have studied polymorphisms of other serotonin receptor subtypes. Reynolds and colleagues found a relationship between 5HT1A receptor polymorphism (−1019C/G) with the response to antipsychotic drug treatment, for negative and depressive symptoms, but not for positive symptoms (Reynolds et al., 2006). Polymorphisms of other 5HT receptor subtypes such as 5-HT2C (Malhotra et al., 1996b; Masellis et al., 1998; Rietschel et al., 1997; Sodhi et al., 1995), 5-HT3A (Gutierrez et al. 2002), 5-HT6 (Masellis et al., 2001; Yu et al., 1999) and 5-HT7 (Masellis et al., 2001) as well as the serotonin transporter 5HTT gene (Arranz et al., 2000a; Tsai et al., 2000) did not show a significant relationship with clinical response to clozapine treatment, however.

Arranz and colleagues used published data to generate a genetic profile of serotonin receptor polymorphisms to predict treatment response (Arranz et al., 2000a). They reported a combination of 6 polymorphisms that yielded a sensitivity of 95% and a specificity of 76%, in predicting response to clozapine although a different group failed to replicate these findings (Schumacher et al., 2000), a discrepancy explained by Arranz and colleagues as being due to differences in methodology and in ethnicity of the study populations (Arranz et al., 2000b).

Glutamatergic system

With growing evidence for the involvement of glutamate dysfunction in schizophrenia (Stone et al., 2007), there has been interest in whether NMDA receptor or other glutamatergic abnormalities might explain the lack of response to dopaminergic antipsychotic drugs. It has also been suggested that clozapine might have downstream effects on NMDA receptor function, perhaps explaining its favourable clinical profile (Schwieler et al., 2008). So far, there have been relatively few genetic studies examining treatment response in relation to glutamatergic neurotransmission, however. Two studies failed to find a correlation between polymorphisms of the NR2B subunit of the NMDA receptor (GRIN2B) and treatment response (Chiu et al., 2003; Hong et al., 2001). In contrast, a study of the metabotropic receptor gene GRM3 found a relationship with negative symptom response to olanzapine treatment, but this finding has yet to be replicated (Bishop et al., 2005).

Norepinephrine system

Adrenergic alpha 1A and alpha 2A antagonists have been reported to improve psychotic symptoms when combined with antipsychotic drugs (Litman et al., 1996). It has been suggested that the effect of clozapine blocking alpha-2 receptors may explain its superior efficacy (Brunello et al., 1995). Two studies assessed the link between norepinephrine polymorphisms and clozapine response, Tsai and colleagues examined a polymorphism of the promotor region of the alpha 2A-adrenoreceptor gene (Tsai et al., 2001), and Bolonna and colleagues studied a polymorphism of the alpha-1A receptor (Arg492Cys) (Bolonna et al., 2000). Neither study found a significant relationship.

Summary

To date there has been no conclusive evidence supporting a genetic basis for antipsychotic response. Many of the initial reports of positive findings occurred in studies of small sample size, and when repeated with larger and better-designed studies, or in groups of different ethnicities, it was not possible to replicate these initial findings. It is likely that treatment resistance may be affected by epigenetic factors, with gene × gene and gene × environment interactions both playing a role. Non-response to antipsychotic drugs, as with schizophrenia, might thus arise from multiple genes of small effect size, and be influenced by non-genetic factors including stress and duration of untreated psychosis. Nonetheless, there is still the slight possibility that a single gene with a large effect on antipsychotic treatment response may exist: many likely candidate genes have not yet been studied in relationship to treatment response, and further work, informed by findings from other fields of research, is required.

Peripheral markers of treatment response

Catecholamine metabolites

Patients with schizophrenia are thought to have increased dopaminergic activity and have been reported to have increased plasma homovanillic acid (pHVA), the principle dopamine metabolite (Pickar et al., 1984). Since a substantial percentage of circulating HVA originates from the CNS, pHVA is a putative marker of changes in central DA levels (Amin et al., 1995; Kendler et al., 1982).

Bowers et al. (1984) reported that pHVA levels before and during the first week of treatment could both predict response to treatment. Good responders had higher mean pHVA values than poor responders. This finding was replicated by several groups (Chang et al., 1990; Kaneda et al., 2005; Koreen et al., 1994; Mazure et al., 1991; van Kammen et al., 1996; Yoshimura et al., 2003). A similar relationship with plasma levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (pMHPG) was also reported by some (Bowers et al., 1984; Koreen et al., 1994; van Kammen et al., 1996), but not all (Yoshimura et al., 2003), studies.

Sumiyoshi et al. (1997) found that pre-treatment pHVA correlated with short-term (six weeks to three months), but not long-term outcomes (six months) for clozapine-treated patients. Another study found lower pre-clozapine pHVA correlated with improvement in negative symptomatology (Brown et al., 1997). Green and colleagues found that pHVA level and pMHPG level decreased during the initial week of clozapine treatment in responders but not in non-responders and plasma levels of DA and NE increased in both responders and non-responders (Green et al., 1993b).

Pickar and colleagues reported a correlation between psychosis rating and pHVA both during five weeks' placebo and five weeks of fluphenazine treatment. Those subjects with a more marked reduction in pHVA on fluphenazine showed the greatest improvement in symptoms (Pickar et al., 1986). Three groups reported an early increase in pHVA levels up to day 4 after the initiation of treatment, followed by a decrease up to 28 days, finding that the magnitude of change for both the early increase and subsequent decline correlated with treatment response at 28 days (Davila et al., 1988; Duncan et al., 1993; Green et al., 1993a). Several other studies have found a similar relationship between reduction in pHVA and pMHPG and treatment response (Bowers et al., 1989; Nagaoka et al., 1997).

A few studies failed to fully replicate these findings. One relatively small study did not find a relationship between pretreatment pHVA and subsequent response to haloperidol, although rate of response did correlate with reductions in pHVA (Petrie et al., 1990). A larger, well-designed study of treatment with trifluoperazine (Javaid et al., 1990) did not find any relationship between reductions in pHVA and response. Another group, sampling CSF rather than plasma, found an increase, rather than a decrease, in HVA with olanzapine treatment. In this study, the change in HVA from baseline did not correlate with change in PANSS scores, although higher CSF HVA after treatment was significantly correlated with less severe negative symptom scores (Scheepers et al., 2001). Davidson and colleagues found that although there was a trend for mean pHVA concentrations to reduce to a greater extent in responders during treatment with clozapine, this did not reach statistical significance (Davidson et al., 1993). These discrepant findings in generally well-designed studies suggest that the relationship of pHVA to treatment response is not present in all patients with schizophrenia, and adds to the evidence that the clinical syndrome termed schizophrenia is likely to have a variety of underlying neurochemical bases.

Apomorphine challenge

Inhibition of prolactin release through dopamine receptor stimulation following apomorphine injection has been suggested as a marker of dopamine function (Meltzer et al., 1984). Lieberman et al. (1994) found that a greater decrease in prolactin levels and increase in growth hormone levels following apomorphine stimulation prior to antipsychotic treatment (suggesting enhanced dopamine responsiveness) were associated with subsequent therapeutic response to clozapine. Furthermore, once on clozapine treatment, a smaller decrease in prolactin following apomorphine stimulation was associated with therapeutic response.

Further work explored the potential of clozapine to suppress apomorphine-induced effects on prolactin and growth hormone release, finding inhibition of these effects correlated directly with treatment response (Szymanski et al., 1995). It was concluded that despite a modest action against D2 receptors, D2 blockade is still likely to be required for clinical response to clozapine, while actions at other receptors are likely to underlie its superior efficacy compared with other antipsychotics.

Glutamate

Two groups have investigated the hypothesis that treatment non-response in schizophrenia might be related to glutamatergic abnormalities by measuring plasma glutamate. Alfredsson and Wiesel (1990) found higher levels of plasma glutamate and glutamine in non-responders to sulpiride prior to treatment, but another group found that although plasma glutamate levels were higher in patients with schizophrenia, and correlated with negative symptoms, they did not predict outcome (van der Heijden et al., 2004). It should, however, be borne in mind that plasma glutamate levels are unlikely to closely reflect regional cortical glutamate concentrations (Shulman et al., 2006).

Serotonin

Mohr et al. (1998) used D-fenfluramine (a drug leading to serotonin reuptake inhibition, enhanced serotonin transmission and serotonin-induced downstream prolactin release) to study the relationship of serotonin function to treatment response in patients with schizophrenia. They found that unmedicated patients who had the weakest prolactin response to a D-fenfluramine challenge made the best response to subsequent haloperidol treatment. They suggested that serotonergic dysfunction (excess serotonin release) might underlie non-response to FGAs.

In keeping with this finding, patients with schizophrenia showing the greatest increase in ACTH levels following administration of m-chlorphenylpiperazine (MCPP), a potent 5HT receptor agonist, were found to respond best to clozapine, and the magnitude of ACTH release was found to correlate with the degree of improvement in symptoms (Kahn et al., 1993). Furthermore, Curtis and colleagues found that clozapine attenuated the D-fenfluramine response, and that this correlated directly with clinical improvement (Curtis et al., 1995; Jones et al., 1998).

These findings suggested that the superior efficacy of clozapine compared with FGAs might reflect differences in its effect on the serotonergic system. A study of olanzapine (which has relatively potent 5HT antagonism) also showed attenuation of D-fenfluramine response correlating with symptom improvement (Jones et al., 2002).

Another group, investigating non-responders to 5HT-blocking SGAs, found that they had reduced serotonin in plasma and platelets prior to treatment (van der Heijden et al., 2004). Together, these data suggest that there may be at least three neurochemical abnormalities in different groups of patients with schizophrenia; patients with excess dopamine release, who respond well to FGAs, patients with excess serotonin release, who respond well to 5HT-blocking SGAs, and a third group, with low plasma serotonin, who respond to neither FGAs or SGAs. Further work is required to investigate this possibility.

Dexamethasone suppression test

Several studies have reported a higher rate of non-suppression following dexamethasone suppression test (DST) in patients with schizophrenia compared with non-psychiatric controls (Banki et al., 1984; Dewan et al., 1982; Sharma et al., 1988; Tandon et al., 1991; Yeragani, 1990). Some groups have found that DST non-suppression was related to depressive (Carroll et al., 1981; Munro et al., 1984) or negative symptoms (Addington and Addington, 1990; Coppen et al., 1983), whereas others found no such associations (Garyfallos et al., 1993; Yeragani, 1990).

Two groups (Ceskova et al., 2001; Yazici et al., 2002), have found that patients with schizophrenia responding to treatment had a higher rate of DST non-suppression compared with treatment non-responders. Ceskova et al. (2002) also found that baseline cortisolaemia after the administration of dexamethasone was predictive of long-term treatment outcome. In contrast, an earlier study found DST non-suppression after 4 weeks antipsychotic treatment was associated with non-response to antipsychotic treatment (Tandon et al., 1991).

Summary

The strongest finding in studies of peripheral markers has been the relationship between elevated baseline pHVA and treatment response. This suggests that those subjects who have the most perturbed dopaminergic transmission are those who will respond most fully to antipsychotic drugs acting through D2 blockade. There is also growing evidence that elevated serotonin may be associated with non-response to FGAs and that low plasma serotonin might be associated with non-response to SGAs with action at 5HT receptors. Replication of these findings is required.

Neuroimaging associations with treatment response

Structural brain imaging

It was initially hypothesised that differential response to antipsychotic drugs might be explained by 'brain morphological differences'. This was based on the theory that schizophrenia could be divided into two distinct subtypes; type I characterised by florid positive psychotic symptoms, and a good response to antipsychotic medication; and type II presenting with a clinical picture comprising mainly negative symptoms, with marked structural brain changes and being poorly responsive to medication (Crow, 1980).

Initial findings were very promising. Weinberger et al. (1980) found that that patients who had enlarged ventricles showed no clinical improvement on antipsychotic drugs, whereas patients with normal sized ventricles responded to medication. Following this, a large number of studies tried

to replicate this finding. Although several were positive, there were also a large number of negative studies, and a review in 1992 concluded that overall there was little support for the hypothesis that brain structural changes predict antipsychotic response (Friedman et al., 1992). A later study using a more sophisticated method found a correlation with cortical grey matter volume and treatment response, with patients showing a response to lower doses of haloperidol having larger grey matter volume, but this has yet to be replicated (Zipursky et al., 1998).

One group studied the predictive value of combining measurement of ventricle size with clinical variables and dexamethasone suppression test. They found that subjects with the highest levels of baseline psychopathology showed the greatest response to treatment, but that subjects with enlarged ventricles or non-suppression on DST had greater variation in baseline symptoms and more unpredictable response to treatment (Mauri et al., 1994).

Other studies examined the relationship between individual brain structures and treatment. One group reported that individuals with greater hippocampal volume responded more readily to risperidone treatment (Savas et al., 2002), whilst Molina and colleagues failed to replicate this finding (Molina et al., 2003a), but found that subjects with smaller orbitofrontal volumes were more likely to have positive symptoms responsive to olanzapine (Molina et al., 2004).

In contrast, a double-blind placebo-controlled study of poor responders to antipsychotic treatment found that larger right prefrontal grey matter volume was associated with better treatment response (improvement in negative symptoms) in patients randomised to clozapine, but poorer response (worsening of BPRS total score) in patients randomised to haloperidol (Arango et al., 2003). Molina and colleagues replicated the finding of correlation between increased prefrontal cortex volume and improvement in negative symptoms in clozapine treated patients, and also found that temporal cortex volume correlated with improvements in positive symptoms (Molina et al., 2003b).

Functional imaging studies

Several groups have employed positron emission tomography (PET) and SPECT to study blood flow and brain metabolism in treatment resistant patients. One group using [18F]FDG PET reported lower relative striatal metabolic rates in the striatum of responders compared with non-responders (Buchsbaum et al., 1992). When treated with haloperidol, the relative metabolic rate increased, with a larger increase in responders. Another group using SPECT imaging found that poor responders to clozapine had significantly lower perfusion in thalamus, left basal ganglia and right prefrontal regions prior to treatment (Molina Rodriguez, et al., 1996). A further SPECT study in non-responders to risperidone who were subsequently successfully treated using clozapine found that clinical response correlated with an increase in thalamic perfusion (Molina et al., 2008). An earlier SPECT study had not shown any difference in perfusion between good and poor responders to antipsychotic drugs, although it did find that non-responders had lower volumes of most brain structures, and performed worse on episodic memory tests (Lawrie et al., 1995).

Neurochemical imaging studies

A SPECT study of responders and non-responders following FGA treatment found that they did not differ in terms of striatal dopamine receptor occupancy (Pilowsky et al., 1993). This is consistent with the notion that patients with schizophrenia respond well to antipsychotic treatment may have a primarily dopaminergic abnormality, whereas poor responders might have a non-dopaminergic basis to their symptoms. This hypothesis was supported by work from Abi-Dargham and colleagues showing that higher levels of baseline synaptic dopamine (as indexed by occupancy of striatal receptors by a D2 ligand) predicted good treatment response (Abi-Dargham et al., 2000).

A recent study replicated the earlier finding of haloperidol responders and non-responders having no difference in striatal D2 receptor occupancy (Corripio et al. 2005). However, this study also reported that non-responders to ziprasidone had lower striatal D2 receptor occupancy (50% compared with 69%) despite taking similar doses to responders (Corripio et al. 2005). This suggests that treatment resistance to ziprasidone might relate to individual pharmacokinetic differences since a minimum striatal occupancy of 65% has been hypothesised to be required for a clinical response to non-clozapine antipsychotic drugs (Kapur and Remington, 2001).

Unfortunately, no other receptor imaging studies have been performed to date studying non-responders, but two groups found a correlation between striatal dopamine receptor occupancy and reduction in symptoms when patients who responded well to antipsychotic drugs were treated with high and low doses of risperidone and olanzapine (Agid et al., 2007; Catafau et al., 2006).

Grunder and colleagues used [18F]DOPA to study the effect of haloperidol on presynaptic dopamine synthesis. They found that subchronic haloperidol treatment led to a reduction in striatal and thalamic [18F]DOPA uptake, and that the reduction in thalamic [18F]DOPA uptake correlated with improvement in negative symptoms (Grunder et al., 2003). This finding gives evidence that haloperidol has an effect on presynaptic dopamine synthesis capacity, and suggests that this aspect of its function may be involved in symptom reduction. By extension, it suggests that poor responders to antipsychotic drugs may show less change in thalamic [18F]DOPA uptake following haloperidol treatment, but a study of non-responders is required to test this hypothesis.

Goff et al. (2002) used magnetic resonance spectroscopy (MRS) to study changes in anterior cingulate glutamate and glutamine (Glx) following a switch from FGAs to olanzapine. They found that anterior cingulate Glx reduced in subjects who showed no improvement in negative symptoms following the switch, but increased in subjects showing a reduction in negative symptoms, suggesting a differential effect of antipsychotic drugs on anterior cingulate glutamatergic transmission in good and poor responders, and implicating glutamate in this region in negative symptoms. Another group found that treatment with risperidone led to an increase in thalamic N-acetyl aspartate (NAA) and myoinositol, but did not find a relationship with treatment response (Szulc et al., 2005). Interestingly, this study found a correlation between negative

symptoms and temporal cortex Glx at baseline. These studies used 1.5-Tesla MRI scanners, which are of relatively low field strength to accurately measure glutamate and Glx using MRS. Further work using MRS to examine neurochemical changes and treatment response would be of benefit.

Summary

The data from neuroimaging studies of treatment response in schizophrenia have been inconsistent. However, there is fairly good evidence responders and non-responders have the same levels of dopamine receptor occupancy by antipsychotic drugs when treated at standard therapeutic doses, although ziprasidone may be an exception to this. There is intriguing preliminary evidence that glutamatergic abnormalities may underlie negative symptoms unresponsive to first generation antipsychotic drug treatment, but replication of this finding is required, and further work is needed to elucidate the role of different neurotransmitters in symptom production and treatment response in patients with schizophrenia.

Discussion

Non-response to antipsychotic drugs is a fundamental problem in psychiatric practice, but the underlying causes of good and poor response to antipsychotic drugs remain unclear. Studies so far have not used the optimum design to study this question. They have mainly investigated chronic patients, with potential confounds from varying duration of untreated psychosis and different medication history. Moreover, treatment has primarily been delivered in a naturalistic manner, and ratings of response have often been retrospective, and measured with clinical interview, rather than with standardised instruments. Patients with first episode schizophrenia generally show a better response to antipsychotic treatment (Perkins et al., 2005), and chronic illness may include potentially irreversible damage arising with disease progression (Deutsch et al., 2001; Lieberman, 1999). There is thus a clear need for well-designed prospective studies of standardised treatment in untreated first episode patients, particularly in the field of neuroimaging and pharmacology, to address this important clinical and research question adequately.

Theoretical models of non-response and potential targets for new treatments

Although research to date is still far from conclusive, the weight of evidence is consistent with the broad hypothesis that antipsychotic responders have marked dopaminergic abnormalities at baseline that are partially normalised by antipsychotic treatment. Non-responders have still not been well characterised in terms of neurochemical profile, and the hypothesis that in these patients the disorder is particularly associated with changes in neurotransmitters other than dopamine remains to be tested.

Studies of peripheral markers suggest there may be a serotonergic abnormality in non-responders. One study

suggested that reduced plasma and platelet 5HT levels could predict non-response to four SGAs, all of which had potent action at 5HT receptors (van der Heijden et al., 2004). It would be interesting to replicate this finding, and also to determine whether reduced plasma and platelet 5HT levels could also predict non-response to clozapine. If subjects with low plasma and platelet 5HT were found to respond to clozapine, it would help to narrow down the aspect of clozapine's action that makes it more efficacious than other antipsychotic drugs.

Given the increasing evidence for glutamatergic abnormalities in schizophrenia, and the close interaction between glutamate and dopamine, a more severe glutamatergic abnormality (which would not be amenable to treatment with dopamine blocking drugs) in non-responders makes intuitive sense. There are only a few studies supporting this hypothesis at present, although there is a growing body of work associating glutamatergic abnormalities with negative symptoms (Pilowsky et al., 2006; Stone et al., 2008b; Szulc et al., 2005), which are often refractory to treatment (Buchanan et al., 1998; Javitt, 2001; Tamminga et al., 1998). Drugs which enhance NMDA receptor function have generally shown improvement in negative, rather than positive symptoms (Javitt, 2006; Tuominen et al., 2005), while a recently developed antipsychotic drug with a novel mechanism of action through metabotropic glutamate receptors (LY2140023), has been found to have efficacy against negative as well as positive symptoms (Patil et al., 2007). A key conceptual issue for glutamatergic intervention may be that the response depends on the stage of the disorder that the treatment is administered. Neuroimaging studies of glutamate function suggest that the pattern of abnormalities changes with the course of the disorder, with differences between the prodromal, first episode and chronic phases (Stone et al., 2007). Glutamatergic treatments may thus be particularly effective in the early phase of illness. This possibility has yet to be tested.

Conclusions

Non-response to antipsychotic drugs remains a significant clinical problem in the treatment of patients with schizophrenia. Drugs that target dopamine D2 receptors are unlikely to improve outcome for non-responders as the underlying pathophysiology may involve other neurochemical abnormalities that are unaffected by existing antipsychotics. Although there is some limited evidence that lack of treatment response might be secondary to serotonergic or glutamatergic abnormalities, further work is required to characterise the basis of treatment refractoriness in schizophrenia. Neurochemical imaging studies targeting the prediction of treatment response in the first episode are required to investigate the neurochemical basis of antipsychotic response with the minimum of confounding variables. Such studies, employing methods such as PET, SPECT and MRS, are likely be of great utility in identification of new targets for antipsychotic drugs or augmentative treatments. In the future such imaging techniques may also be of use in choosing the most appropriate treatment for a given patient.

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