Published in final edited form as:

Curr Pharm Des. 2009 ; 15(22): 2550–2559.

Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging

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Abstract

Molecular imaging studies have generated important *in vivo* insights into the etiology of schizophrenia and treatment response. This article first reviews the PET and SPECT evidence implicating dopaminergic dysfunction, especially presynaptic dysregulation, as a mechanism for psychosis. Second, it summarises the neurochemical imaging studies of antipsychotic action, focussing on D2/3 receptors. These studies show that all currently licensed antipsychotic drugs block striatal D2/3 receptors *in vivo*—a site downstream of the likely principal dopaminergic pathophysiology in schizophrenia—and that D2/3 occupancy above a threshold is required for antipsychotic treatment response. However, adverse events, such as extra-pyramidal side-effects or hyperprolactinemia, become much more likely at higher occupancy levels, which indicates there is an optimal ‘therapeutic window’ for D2/3 occupancy, and questions the use of high doses of antipsychotic treatment in clinical practice and trials. Adequate D2/3 blockade by antipsychotic drugs is necessary but not always sufficient for antipsychotic response. Molecular imaging studies of clozapine, the one antipsychotic licensed for treatment resistant schizophrenia, have provided insights into the mechanisms underlying its unique efficacy. To link this pharmacology to the phenomenology of the illness, we discuss the role of dopamine in motivational salience and show how i) psychosis could be viewed as a process of aberrant salience, and ii) antipsychotics might provide symptomatic relief by blocking this aberrant salience. Finally, we discuss the implications of these PET and SPECT findings for new avenues of drug development.

Keywords

schizophrenia; psychosis; mechanisms; treatment; antipsychotic; imaging; etiology; PET

Introduction

Schizophrenia is amongst the most common of the severe mental illnesses [1;2], and one of the top ten causes of global disease burden amongst adults [3]. It is a chronic psychotic disorder with a lifetime prevalence of about 0.7%, primarily affecting adults, and having a

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Declaration of interest:

ODH, PM and SK have all received investigator led charitable research funding and speaker engagements from most manufacturers of antipsychotic medications. None of the authors have any other potential conflicts of interests.

peak age of onset in the early twenties in men, and three or four years later in women [4]. Women show a later second peak around the time of the menopause, although the lifetime risk for men and women is about equal [4]. In addition to considerable morbidity and high mortality rate associated with schizophrenia, the health and social care costs for the illness are substantial: equivalent to about 1.6% of the health care budget in the United Kingdom each year, for example [5-7].

There are no pathognomic features, or definitive diagnostic tests, for schizophrenia and its symptoms may be seen in other physical or mental illnesses [8]. The typical symptoms have been categorised into 'positive' and 'negative' symptom clusters. 'Positive symptoms', such as hallucinations, delusions and thought disorder, are features of psychosis, whilst alogia, apathy, anergia, and self-neglect are typical of 'negative symptoms' [9]. Schizoaffective disorder is a related psychotic illness, characterised by the co-occurrence of schizophrenic symptoms with evidence of significant affective disturbance. There is considerable overlap between schizophrenia and schizoaffective disorder in terms of symptomatology and treatment [10].

The pathophysiological basis of schizophrenia is complex, and remains incompletely understood [11;12]. However, better understanding the molecular processes underlying the symptoms of the illness is likely to be essential for improving the use of current drug treatments and to develop new and preventive therapies-as has recently been highlighted [13;14].

The most enduring neurochemical theory of schizophrenia centres upon dysregulation of dopaminergic neurotransmission [15]. All currently licensed antipsychotic drugs block dopamine receptors, indicating that manipulation of dopaminergic function is fundamental to therapeutic response in psychosis. Positron emission tomography (PET) and the related technique of single positron emission computerised tomography (SPECT) provide unique opportunities to explore molecular aspects of dopaminergic function in the brain of schizophrenic patients *in vivo*. This review first describes the recent advances arising from PET and SPECT studies in understanding the nature of dopaminergic abnormalities in schizophrenia, and then focuses on the new insights which molecular imaging studies have provided into antipsychotic mechanisms and treatment response.

The pathoetiology of schizophrenia: dopamine's role

The idea that dopaminergic abnormalities might be linked to schizophrenia initially arose from several indirect sources of evidence. One major observation was that administration of the psychostimulant amphetamine, which increases extracellular concentrations of dopamine, can induce psychotic symptoms akin to those seen in schizophrenia (see review [16]). Additional evidence came from studies of reserpine. Reserpine blocks the reuptake of dopamine, leading to its dissipation [17], and, although not a licensed treatment, is an effective therapy for treating psychosis-indeed plant based therapies containing reserpine have been used for centuries in India as treatments for illnesses that would now be classified as schizophrenia. Key evidence for dopamine's involvement in treatment response came in the 1970s, when the clinical effectiveness of antipsychotic drugs was found to directly relate to their affinity for dopamine receptors [18;19]. As a result of this discovery, the leading hypothesis at this time was that schizophrenia may arise as a result of abnormalities in dopamine receptor density, and that psychosis may be treated through pharmacological blockade of these receptors [20;21].

Whilst these findings implicated dopamine in schizophrenia, this was in a rather general way and there were a number of limitations on the interpretation of the evidence. For example, both amphetamine and reserpine affect other brain monoamines as well as dopamine, and

subsequent post-mortem findings of brain dopamine D2 receptor densities and dopamine levels in people with schizophrenia were inconsistent (see review [22]). Furthermore, at this time there was no clear indication of the locus of dopaminergic abnormality in the living brain, nor the mechanism by which dopaminergic dysfunction may be related to clinical symptoms.

PET and SPECT imaging allows quantification of the rate of uptake and degree of specific binding of radiolabelled compounds in the human brain *in vivo*. The availability of selective dopaminergic radiotracers allows inspection of the key stages in the pathway of dopaminergic synaptic transmission, including capacity for presynaptic dopamine synthesis, the degree of dopamine release in response to stimuli and concentration of extracellular dopamine, and the density and availability of the post-synaptic dopaminergic receptors. Over the last decade or so, the considerable advances in PET/SPECT technology and increasingly widespread application of this technique has enabled the major aspects of the dopaminergic hypothesis of schizophrenia to be tested and refined.

Dopamine synthesis and release

Presynaptic dopaminergic availability can be measured using PET imaging with radiolabelled L-dihydroxyphenylalanine (L-DOPA). In the brain, radiolabelled L-DOPA is converted to dopamine and trapped in dopaminergic nerve terminals. The extent of radiolabelled L-DOPA uptake thus provides an index of presynaptic dopamine synthesis capacity and the availability of dopamine for release from presynaptic terminals (see review [23]). To date, there have been nine PET studies of dopaminergic availability in patients with schizophrenia; seven have found elevated levels of dopamine synthesis capacity in the striatum of schizophrenic patients compared to control subjects (see summary table 1 adapted from the review by Howes et al) [24]. In all studies where patients were acutely psychotic at the time of investigation elevated presynaptic striatal dopamine availability was detected [25-28]. Furthermore, it has recently been demonstrated that dopamine synthesis is also increased in patients with prodromal symptoms of schizophrenia, prior to the onset of psychosis [28]. At present, increased striatal presynaptic dopamine availability is the most widely replicated brain dopaminergic abnormality in schizophrenia, and the effect size is moderate to large (0.63-1.25) [24].

The next step in dopaminergic neurotransmission is the release of dopamine. PET or SPECT imaging with radiotracers which bind dopamine D2 receptors, such as [¹¹C]raclopride or [¹²³I]IBZM, may be used to index striatal dopamine release, as these radiotracers compete with dopamine to bind to dopamine D2 receptors. Decreases in radiotracer binding are thereby interpreted as reflecting increases in extracellular dopamine. For studies of this type, a pharmacological challenge of a dopamine-releasing drug, such as amphetamine, may be applied to probe dopamine release capacity. Using this approach, three investigations have found evidence of increased dopamine release in patients with schizophrenia compared to control subjects [29-31]. The extent of radiotracer displacement was approximately doubled in schizophrenic patients, and the degree of displacement correlated with the degree of worsening of psychotic symptoms. A SPECT study using a dopamine depletion technique has also found that baseline occupancy of D2 receptors by dopamine is increased in schizophrenia, indicating that extracellular dopamine concentrations are also increased at baseline [32]. Together, these studies provide compelling evidence that presynaptic dopamine availability and dopamine release are increased in schizophrenia. Although at a lower level, increased dopamine availability and release has also been observed in subjects who are at increased risk of developing schizophrenia and who experience mild schizophreniform symptoms, suggesting this dopamine dysregulation may also underlie the development of the illness [28;33].

Dopamine D2 Receptors

The action of dopamine on post-synaptic receptors constitutes the final stage in transmitting the dopaminergic neuronal impulse to post-synaptic neurons. As all clinically available antipsychotics block D2 receptors, over the last two decades many studies have investigated whether D2 receptor density is altered in schizophrenia compared to control subjects. There have been at least nineteen published studies, but, after an initial positive finding, subsequent results have been inconsistent [34]. This is probably due to a number of factors, particularly the inclusion of antipsychotic treated patients in the initial and some subsequent studies, the properties of the different radiotracers used and baseline concentrations of extracellular dopamine [34]. It is also worth noting that, due to lack of pharmacological specificity of the radiotracers, there is generally some additional contribution from D3 receptor binding in these studies. Three published meta-analyses [34-36] conclude that D2/3 density shows marked heterogeneity in schizophrenia, and, although there may be an elevation in striatal D2/3 receptor density, perhaps in a subgroup of patients, it is moderate (10-20%) at most. This elevation appears to be specific to D2/3 receptors - striatal D1 receptor densities are unaltered [34;35;37;38]. Fewer studies have investigated D2/3 receptor density in extrastriatal brain regions in schizophrenia, but current evidence suggests that the density of D2/D3 receptors may be decreased in areas such as the thalamus and anterior cingulate cortex [39-42]. Finally, the D2 receptor may exist in two intraconvertible (high and low) affinity states for agonist binding and it remains to be determined if the balance between these two states is altered in schizophrenia [43], although preliminary data suggests that no alteration is apparent in the absence of dopamine depletion [44].

Making sense of the dopaminergic dysfunction in schizophrenia and linking it to symptoms

It is apparent from the studies reviewed above that the initial hypothesis that abnormalities in D2 receptor densities underlie schizophrenia has not been convincingly supported by PET and SPECT studies. Rather, the data show schizophrenia is characterised by elevated presynaptic dopamine availability and release in the striatum. What is not apparent from these data is the process by which these molecular abnormalities in striatal dopamine function translate to the symptoms of schizophrenia that are observed in the clinic.

A model has recently been described [15;45] which seeks to explain the translation of presynaptic dopaminergic abnormalities to psychotic symptoms. Underlying this hypothesis is an extensive animal literature which describes a central role of dopamine in learning the predictive contingencies between the presence of environmental stimuli and rewarding or aversive events. Specifically, dopamine is thought to mediate the assignment of motivational salience to internal or external stimuli, thus increasing the propensity for these stimuli to grab attention and drive behaviour. Normally, motivational salience is applied to stimuli which are relevant in terms of their contingency with pleasurable or unpleasant outcomes. The hypothesis proposes that in schizophrenia, where presynaptic dopaminergic function is elevated, dopamine release may occur in the absence of relevant stimuli. This stimulus-independent dopamine release would result in assignment of salience to other, normally irrelevant, stimuli whose presence happens to temporally coincide with dopamine release. This process is termed aberrant attribution of salience, and may underlie clinical phenomena such as the propensity for patients to begin to attach special meaning to events that were previously unremarkable. Eventually, aberrant salience may form the basis of psychotic symptoms; delusions, for example, develop from the individual's cognitive effort to make sense of these experiences, and thus reflect personal and cultural interpretations. This model, illustrated in figure 1, is consistent with a number of clinical phenomena, such as patient reports that their psychosis first began with an increasing sense that something unusual was

going on around them. As described below, aberrant salience may also explain some treatment effects.

The PET and SPECT findings described above, together with new animal and other evidence, have led to the proposal of a revised ‘version III’ of the dopamine hypothesis of schizophrenia [46]. This dopamine hypothesis integrates recent findings on risk factors for schizophrenia with the neurochemical findings and the aberrant salience model discussed above. It proposes that multiple environmental and genetic ‘hits’ interact to result in dopaminergic dysfunction - the final common pathway to psychosis and the diagnosis of schizophrenia.

Insights into mechanisms underlying treatment response and side-effects

Antipsychotic drugs and dopamine D2 receptors

Although all currently licensed antipsychotic drugs block D2 dopamine receptors, they also act at a number of other neurotransmitter receptors in the brain, including other dopamine receptor subtypes and those for serotonin, histamine, norepinephrine and acetylcholine. Given this rich pharmacology, it was initially far from clear which receptor mediated the clinical response to antipsychotic treatment. Landmark *in vitro* studies in the 1970s showed there was a close relationship between the affinity of antipsychotic drugs for D2 receptors and the clinical potency of the drugs [18;19]. Subsequent ligand imaging studies with both SPECT (eg: [47-51]) and PET (eg: [52-58]) have demonstrated that all antipsychotic drugs cross the blood-brain-barrier and block D2/3 striatal receptors *in vivo* at clinically effective doses. These data support the *in vitro* findings, and have provided the foundation for studies in which the relationship between D2 occupancy and clinical response could be established.

D2 occupancy and clinical response

Interestingly, initial PET and SPECT studies found no relationship between D2 receptor occupancy and clinical response (see, for example, [59]). However, it has subsequently transpired that this was the first clue to a curious property of the relationship between antipsychotic drug occupancy of D2 receptors and clinical response - it appears to be non-linear. The early studies generally used moderate to high antipsychotic drug doses which resulted in levels of D2 occupancy greater than 65% [59]. More recent studies including low doses of antipsychotics indicate that there is little clinical response seen when occupancy is less than 50%, with clinical response increasing from this point [60]. This suggests that a therapeutic threshold of D2 occupancy is required for clinical response to antipsychotic drugs. This hypothesis has specifically been investigated in a double blind study of patients experiencing their first episode of schizophrenic psychosis [61]. D2 receptor occupancy was determined with [¹¹C]raclopride PET imaging following two weeks of antipsychotic treatment and clinical response assessed in the patients. The results confirmed that clinical efficacy requires a threshold of occupancy of D2 receptors. A threshold D2 occupancy of 65% was found to best separate responders from non-responders: at 65% receptor occupancy, 80% of responders were above the threshold whilst 67% of the non-responders lay below the 65% threshold. Receptor occupancy much above 65% was associated with a far higher risk of side-effects (see below) but little further clinical improvement. This is an important finding: in the past, if there was little or no initial response the clinical practice was to keep increasing the antipsychotic dose under the misguided belief that this would increase the chance of a subsequent response. However, these PET findings indicate that in general high doses offer no therapeutic advantages and only increase the risk of adverse events.

Another therapeutic insight provided by PET and SPECT imaging studies is the high level of individual variation in D2 occupancy which occurs (eg: 38%-87%), despite patients

receiving identical doses of the same antipsychotic compound. This variation may partly underlie the large differences in individual response to standard doses of antipsychotic and explain why it can be so difficult to predict the optimal dose of antipsychotic to use. Furthermore, PET imaging studies have provided evidence that some patients show little or no response even though antipsychotic D2 occupancy is well above the therapeutic threshold [62]. Therefore, D2 receptor occupancy above a threshold is necessary for, but not sufficient to guarantee, antipsychotic treatment response.

As illustrated in figure 2, in the context of the aberrant salience model described earlier, blockade of D2 receptors by antipsychotic drugs will dampen the propensity of inappropriate dopamine release to result in aberrantly assigned salience [15;45]. This model is consistent with the observation that existing delusions become less important to patients during antipsychotic treatment, but also the observation that antipsychotic therapy may be associated with dysphoria or a 'deficit-like state'. The relationship between clinical response, side-effects and D2 occupancy is discussed below.

The relationship between D2 occupancy and time to response

Most textbooks of psychiatry state that patients take weeks to show any response to antipsychotic treatment – thus perpetuating the dogma that onset of antipsychotic response is 'delayed'. However this received wisdom is questioned by PET imaging studies which have demonstrated that adequate striatal D2 occupancy occurs within hours of starting antipsychotic treatment [63]. Whilst it is possible that treatment response requires a chain of secondary events occurring after D2 occupancy, such as depolarisation blockade, that may take weeks to occur – the findings have caused the clinical data to be examined more critically. A meta-analysis of nearly 8,000 patients conclusively showed that clinical improvement does occur within the first two weeks of starting regular antipsychotic treatment [64]. In fact, the largest improvement in symptoms may occur over the *first two weeks* of antipsychotic treatment [71]. Furthermore, high D2 occupancy forty-eight hours after starting antipsychotic treatment is significantly associated with a greater clinical response two weeks later [65]. Taken together, these findings suggest that clinical response sets in rather contemporaneously with D2 occupancy – thus strengthening the causal link between the two.

Antipsychotic drug dosing regimes and D2 occupancy

Most oral antipsychotic drug regimens require the patient to take the drug once or twice a day. Antipsychotic dosing schedules are principally designed on the basis of plasma drug concentrations and usually assume a direct relationship between the levels of the drug in plasma and brain. Using PET imaging, Tauscher et al (2007) tested this assumption by giving healthy volunteers a single dose of a commonly used antipsychotic drug (either risperidone or olanzapine) and measuring both the antipsychotic concentrations in plasma and levels of antipsychotic D2 receptor occupancy in the striatum [66]. The concentrations of both drugs declined relatively rapidly in the plasma; the plasma elimination half-life for olanzapine was about 24 hours, whilst that for risperidone was about 10 hours. This plasma elimination profile contrasted markedly to the temporal profile of D2 occupancy, which remained high for much longer; indeed D2 occupancy levels at or greater than the therapeutic threshold were observed at 48 hours. Tauscher et al (2007) also measured antipsychotic D2 occupancy and plasma concentrations in patients with schizophrenia who had received long-term treatment with either olanzapine or risperidone. After the patients stopped their treatment, similar results were observed - plasma antipsychotic drug levels dropped much faster than the level of D2 occupancy in the brain. These data indicate that the plasma and brain kinetics of antipsychotic drugs are not directly related: antipsychotic D2 occupancy in the brain is sustained whilst plasma drug levels decrease much more quickly.

This finding has two potentially important clinical implications. Firstly, these data indicate that determination of antipsychotic concentrations in plasma may not accurately predict optimal dosing schedules, nor accurately indicate whether individual D2 occupancy lies within the therapeutic window. Secondly, these data suggest that it may not be necessary for patients to take their antipsychotic medications as often as is currently advised, although clinical trials are required for full evaluation of any change in the recommended treatment regime.

Sustained versus transient D2 occupancy by antipsychotic drugs

Most treatment algorithms are based on the idea that patients need to take medication following a dosing schedule that will maintain continuous D2 receptor occupancy. This assumption has been tested by using PET to measure D2 occupancy in patients receiving risperidone depot at a time when it was anticipated that drug levels would be at their nadir (immediately *prior* to when the next dose of injection of medication was due) [67]. In the majority of patients at this time-point, D2 occupancy levels were lower than the threshold for D2 occupancy required for clinical response and, despite this, these individuals did not relapse. The implication of this study is that transiently high levels of D2 occupancy may be sufficient to maintain clinical response; indeed a subsequent PET study has also shown that the orally administered antipsychotic quetiapine produces only transiently high levels of D2 receptor occupancy [68]. Studies comparing the effects of transient versus continuous antipsychotic delivery in animal models provide further support for this idea [69]. Transient delivery was found to be more efficacious, both when doses were matched and when a lower dose was used than that given continuously. Furthermore, whilst continuous treatment resulted in an increase in D2 receptor density, transient treatment did not. This suggests that continuous treatment results in compensatory changes, such as D2 up-regulation, that might counteract therapeutic effects, whilst transient treatment may avoid such changes. Together, these findings suggest that high levels of D2 occupancy may only be required briefly in order to achieve and maintain a clinical response, and, furthermore, that a mode of delivery that results in adequate transient D2 occupancy may avoid counterproductive D2 changes.

These findings indicate that the kinetics of D2 binding are as important as D2 occupancy levels for antipsychotic treatment response. However, converting the receptor kinetic findings into treatment recommendations is complex, because any effort at making occupancy transient makes it more susceptible to the impact of any missed doses – which could turn transient into absent occupancy. Nonetheless, these occupancy kinetic studies provide interesting possibilities that merit further investigation.

Mechanisms underlying antipsychotic treatment side-effects

Patients taking antipsychotic drugs can experience a number of distressing side-effects. These include extra-pyramidal side-effects (EPSE) - which may involve involuntary muscle movements or muscle spasms (often of the face or neck) and restlessness, hyperprolactinaemia (which may affect sexual function) and dysphoria (low mood). PET/SPECT imaging has considerably increased understanding of the mechanisms underlying these side-effects, so that clinical practice may move towards minimising their occurrence. A core observation is the close relationship between the occurrence of several major side-effects and the level of D2 receptor occupancy. An initial PET study demonstrating that patients with EPSE have higher antipsychotic D2 receptor occupancy (>80%) than patients without EPSE (<75%) [70] has subsequently been confirmed in double-blind randomised treatment studies [71]. This relationship is also true for prolactin elevation following antipsychotic treatment - higher levels of D2 occupancy increase the likelihood of hyperprolactinaemia [72]. These studies indicate that different side effects may emerge at different threshold levels of D2 receptor occupancy – for example the D2 occupancy level at

which hyperprolactinaemia is highly likely is lower than that for EPSE. Importantly, the D2 occupancy threshold required for treatment response is lower than that at which both EPSE and hyperprolactinaemia emerge. For example, Kapur et al (2000) found that the likelihood of clinical response, hyperprolactinaemia, and EPSE increased significantly as D2 occupancy exceeded 65%, 72%, and 78% respectively. These data show that there is a 'therapeutic window' for D2 occupancy, above which side-effects are more likely without greater efficacy. The clinical take-home message is therefore that antipsychotic drugs should be used at the lowest effective dose. These PET findings also indicate that many antipsychotic drug trials comparing established antipsychotic drugs with newer compounds have used doses of the established drug that are likely to be above its therapeutic window. This may have increased the risk of side-effects for the established compound, thereby biasing outcomes in favour of the newer compound.

A significant proportion of patients taking antipsychotic drugs also complain of a number of subjective side-effects such as dysphoria, generalised unpleasant feelings, low mood or inability to think (see reviews [73;74]). These negative subjective experiences may emerge even after only a few days of administration of very low doses of antipsychotic drugs - for example, 25% of people taking 50mg of chlorpromazine experienced it [75]. In common with EPSE and hyperprolactinaemia, SPECT studies have found a direct link between the level of antipsychotic D2 blockade in the striatum and severity of these dysphoric experiences [76;77]. de Haan et al (2004) reviewed the literature and concluded that there was a window of D2 occupancy of 60-70% above which adverse subjective side-effects became significant [78]. More recently, Mizrahi et al (2007) confirmed, in the first double-blind controlled study, that higher striatal D2 receptor occupancy is associated with increased negative subjective experiences, even in patients taking newer antipsychotic drugs which were thought to be less likely to induce these subjective adverse effects [79]. This study also examined extra-striatal D2 occupancy by the antipsychotic, finding that higher D2 occupancy in temporal cortex and insular regions was also associated with greater levels of these dysphoric experiences. Furthermore, patients reported dysphoric experiences even at relatively low levels of D2 occupancy. This indicates that subjective adverse experiences may be an inevitable consequence of antipsychotic treatment-even with newer drugs.

Treatment refractory schizophrenia: main PET and SPECT findings

About one third of patients with schizophrenia do not respond to antipsychotic treatment (see review [80]) and only one drug, clozapine, has proven efficacy against positive and negative symptoms in these treatment refractory patients [80-82]. Clozapine treatment is generally reserved for patients in whom other medications have failed as it can have serious side-effects, including agranulocytosis and seizures, although it has lower rates of EPSE than most other antipsychotic drugs [82]. Understanding the mechanisms behind clozapine's unique efficacy is important for two reasons: to provide leads for the development of improved antipsychotic drugs that replicate clozapine's efficacy without reproducing its side-effects; and to advance the understanding of the neurobiology of treatment refractory schizophrenia.

Although a number of theories have been proposed to explain clozapine's atypical efficacy and side-effect profile, the two main ones are its limbic selectivity, and blockade of 5-HT_{2A} serotonergic receptors. The limbic selectivity theory suggests that clozapine preferentially blocks D2 receptors in limbic and cortical dopaminergic systems and thus avoids EPSE associated with striatal D2 receptor blockade. Whilst some PET and SPECT imaging studies support this hypothesis [83-85], others do not [86;87]. In addition, as other antipsychotic drugs may show similar profiles of D2 binding [84;88;89] and it is striatal rather than extra-striatal occupancy that appears to predict treatment response [90], the limbic selectivity

theory does not completely explain clozapine's atypicality. Clozapine acts at a wide range of neurotransmitter receptors, but shows a particularly high affinity at 5-HT_{2A} sites; a feature which has been suggested to underlie its efficacy. PET imaging studies have shown high levels of 5-HT_{2A} occupancy during clozapine treatment [91;92], but this is also observed with other second generation antipsychotic drugs, such as risperidone, olanzapine and quetiapine [93-97]. In conclusion, PET and SPECT data suggest that neither limbic selectivity, nor 5-HT_{2A} occupancy can explain the unique efficacy of clozapine in treatment-resistant schizophrenia, although they may explain its different side-effect profile. New avenues of research must therefore be explored to determine the features of clozapine that confer therapeutic advantage. One possibility is that clozapine may be particularly efficacious in regulating presynaptic dopaminergic function, a hypothesis that may be explored using PET studies in man. Alternatively, direct or indirect interactions of clozapine with other neurotransmitter systems, for example the cholinergic or glutamatergic systems, may be the key to its unique efficacy. These hypotheses may also be explored in the future using PET/SPECT imaging with select radiotracers.

Conclusions and Future Directions

This review has highlighted key findings from PET and SPECT studies that have considerably advanced understanding of the pathophysiology of schizophrenia and significantly contributed towards the development of new and improved drug therapies. Striatal dopaminergic dysfunction is a consistent and widely replicated finding in PET and SPECT studies of schizophrenic molecular pathology. Whilst the consistency of these findings suggest that this could lead to a diagnostic test, PET and SPECT scans of dopaminergic function have not proven sufficiently sensitive to be used as such in the past. However, new approaches to interrogating PET imaging data using multivariate inputs and neural network analysis have recently been applied and found to offer high specificity and sensitivity in identifying people with schizophrenia [98]. These developments, together with improvements in scanner resolution, offer encouragement that PET and SPECT imaging may be used diagnostically in the future. It is apparent from this review of the evidence that changes in presynaptic dopamine availability and stimulated dopamine release are consistently reported across different schizophrenic patient populations and experimental settings, whilst alterations in the density of post-synaptic D_{2/3} receptors are less convincing. This implicates presynaptic dopamine availability and release as the major dopaminergic abnormality in schizophrenia. Presynaptic dopamine availability may therefore provide a practical neurobiological marker for investigation of the dopaminergic basis of symptoms and treatment response in schizophrenia.

PET and SPECT imaging has made major contributions to defining the role of D₂ receptor occupancy in therapeutic response to antipsychotic drug treatment. These studies have shown that current antipsychotic drug therapies require D₂ occupancy above a threshold level for clinical efficacy. However, D₂ occupancy at or above the threshold is not sufficient on its own to guarantee response. What has also been realised is that whilst many of the side-effects of antipsychotic drug treatments relate to D₂ occupancy, fortunately, these side effects generally only become significant at occupancy levels higher than those required to elicit a therapeutic response. These findings show that there is a 'therapeutic window' for antipsychotic drug doses, within which therapeutic effects are induced but side-effects are minimised. This provides clinicians with an empirically defined target to aim for in deciding dosing strategies and indicates that, in general, there is no rationale for the use of high doses of antipsychotic drugs, because this increases the risk of side-effects with little or no benefit in efficacy. Another implication of these findings is that many clinical trials of antipsychotic drugs may have used unnecessarily high doses. This is particularly an issue when high doses of an older comparator drug - that are likely to be in the supra-threshold range of D₂

occupancy - have been compared with doses of a newer compound that are likely to be in the therapeutic window. Clearly this sort of dosing protocol may give the new trial drug an outcome advantage, particularly biasing the inferred potential to reducing the risk of side-effects.

In refining understanding of the pathophysiology of schizophrenia and treatment response, the PET and SPECT imaging studies have highlighted a number of potentially fruitful areas for future drug development. In particular, these investigations demonstrate that schizophrenia is characterised by marked increases in presynaptic dopamine availability and release - which may indeed constitute the primary dopaminergic pathology - but all currently available antipsychotic drugs act downstream at D2 receptors on post-synaptic terminals. Significant therapeutic advantage may be gained through development of compounds that act upstream to rectify presynaptic hyperdopaminergia. This, then, is a potentially important avenue for future drug discovery. Some compounds currently under evaluation might offer this potential [99].

The first generation of PET and SPECT studies into schizophrenia have made a significant contribution to understanding of its pathophysiology and to antipsychotic action. However, whilst it is clear that dopaminergic mechanisms are core elements of the molecular pathology of schizophrenia and key determinants of treatment response to current drugs, other neurotransmitter systems and their interactions with dopaminergic function are also likely to be crucially important in schizophrenic pathophysiology and treatment optimisation. It is therefore likely that the next generation of PET/SPECT imaging studies will utilise new radioligands to probe the functionality of non-dopaminergic neurotransmitter systems and that such studies will play a prominent role in the further refinement of our understanding of the neurobiology of schizophrenia and key therapeutic areas, such as treatment resistance.

ABBREVIATIONS

[11C]DOPA	L-[β- ¹¹ C]Dihydroxyphenylalanine
[18F]DOPA	6-[¹⁸ F]fluoro-L-Dihydroxyphenylalanine
[123I]IBZM	[¹²³ I]-(S)-2-hydroxy-3-iodo-6-methoxy-[(1-ethyl-2-pyrrolidiny)methyl]benzamide
A	antipsychotic drug treated
5-HT2A	5-hydroxytryptamine (also known as serotonin) receptor sub-type 2A
C	chronic illness
D1, D2, D3	Dopamine receptor sub-type 1, 2 and 3 respectively
DF	drug free
EPSE	Extrapyramidal side-effects
F	female
FE	first episode of illness
L-DOPA	L-Dihydroxyphenylalanine
M	male
N	naïve to treatment
PET	Positron Emission Tomography

S.D.	standard deviation
SPECT	Single Photon Emission Tomography

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Figure 1. Showing the main dopaminergic abnormalities in schizophrenia and the proposed mechanism linking these to psychotic symptoms

Figure 2.

Showing the action of antipsychotic drugs to reduce dopaminergic transmission and the proposed mechanism linking this effect to the amelioration of psychotic symptoms

Table 1

Summary of the PET studies of the presynaptic striatal dopamine synthesis capacity (adapted from the review by Howes et al [100]). C= chronic illness, FE= first episode of illness, M= male, F= female, N= naïve to treatment, DF= drug free, A= antipsychotic drug treated, S.D.= standard deviation.

Authors	Radio Tracer	Illness length (FE/C)	N patient group (M/F)	N control group (M/F)	Treatment (N/DF/A)	Control group (means + S.D.)	Patient group (means + S.D.)	P	Effect size
(Reith et al. 1994)	[18F] DOPA	C	5 (5/0)	13 (6/13)	4 N, 1 A	100± 23	120± 15	<0.05	0.91
(Hietala et al. 1995)	[18F] DOPA	All FE	7 (4/3)	8 (6/2)	All N	100± 11	117± 20	<0.05	1.54
(Dac-Castellana et al. 1997)	[18F] DOPA	Not listed	6 (6/0)	7 (7/0)	2 N, 4 DF	100± 11	103± 40	n.s.	0.3
(Hietala et al. 1999)	[18F] DOPA	All FE	10(4/6)	13 (8/5)	All N	100± 17	113± 12	<0.05	1.09
(Lindstrom et al. 1999)	[11C] DOPA	All FE	12(10/2)	10 (8/2)	10 N, 2 DF	100± 17	113± 12	<0.05	0.77
(Elkashaf et al. 2000)	[18F] DOPA	C	19 (15/4)	13 (8/5)	9 DF, 10 A	100± 11.7	92.4± 9.7	<0.05	-0.65
(Meyer-Lindenberg et al. 2002)	[18F] DOPA	C	6(5/1)	6 (5/1)	All DF	100± 9.7	119± 9.7	<0.02	1.96
(McGowan et al. 2004)	[18F] DOPA	C	16 (16/0)	12 (12/0)	All A	100± 9.3	115± 8.2	0.001	1.6
(Howes et al. 2009)	[18F] DOPA	FE and C	7 (5/2)	12 (8/4)	All DF (4 N)	100± 8.5	111± 9.1	0.02	1.29