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REVIEW

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Modelling prefrontal cortex deficits in schizophrenia: implications for treatment

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Current treatments of schizophrenia are compromised by their inability to treat all symptoms of the disease and their side-effects. Whilst existing antipsychotic drugs are effective against positive symptoms, they have negligible efficacy against the prefrontal cortex (PFC)-associated cognitive deficits and negative symptoms. New models that reproduce core pathophysiological features of schizophrenia are more likely to have improved predictive validity in identifying new treatments. We have developed a NMDA receptor antagonist model that reproduces core PFC deficits of schizophrenia and discuss this in relation to pathophysiology and treatments. Subchronic and chronic intermittent PCP (2.6 mg/kg i.p.) was administered to rats. PFC activity was assessed by 2-deoxyglucose imaging, parvalbumin and Kv3.1 mRNA expression, and the attentional set-shifting test (ASST) of executive function. Affymetrix gene array technology was employed to examine gene expression profile patterns. PCP treatment reduced glucose utilization in the PFC (hypofrontality). This was accompanied by a reduction in markers of GABAergic interneurones (parvalbumin and Kv3.1 mRNA expression) and deficits in the extradimensional shift dimension of the ASST. Consistent with their clinical profile, the hypofrontality was not reversed by clozapine or haloperidol. Transcriptional analysis revealed patterns of change consistent with current neurobiological theories of schizophrenia. This model mirrors core neurobiological deficits of schizophrenia; hypofrontality, altered markers of GABAergic interneurone activity and deficits in executive function. As such it is likely to be a valuable translational model for understanding the neurobiological mechanisms underlying hypofrontality and for identifying and validating novel drug targets that may restore PFC deficits in schizophrenia.
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Abbreviations: NMDA, *N*-methyl-D-aspartate; PFC, prefrontal cortex

Introduction

Current treatment of schizophrenia is inadequate because existing antipsychotic drugs do not treat all the symptoms of the disease and produce many side effects. Despite the positive symptoms being alleviated by typical and atypical drugs, the predicted marked improvement of the atypicals over the typicals in the treatment of the negative symptoms and cognitive deficits has failed to be realized (Lieberman *et al*., 2005; Keefe *et al*., 2007). Furthermore, although atypical drugs produce limited extrapyramidal side effects, these drugs can induce other unwanted effects, such as agranulocytosis (clozapine) or weight gain (for example, olanzapine).

In the last decade, evidence has emerged that many cognitive domains are affected in schizophrenia. These include attention, executive function, working memory, visual and verbal learning and memory. Improvements in neurocognitive deficits are reported to be better predictors of social functioning than improvements in psychotic symptoms (Green, 2006). However, evidence for cognitive deficits in the disease has not been paralleled by the introduction of new treatments or clinical trial activity for cognition in schizophrenia. This translational bottleneck has prompted the MATRICS (Measurement And Treatment Research to Improve Cognition in Schizophrenia) and the TURNS (Treatment Units for Research on Neurocognition and Schizophrenia) initiatives. In this respect, one of the major

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challenges is to develop translational preclinical models that are more likely to predict improvements in the cognitive deficits and negative symptoms.

Research in our laboratories has focussed on developing such a translational model. We have incorporated known pathophysiological features of the disease with a cognitive end point and predict that the improved construct validity will lead to the identification of new treatments. By conducting genomic analysis of the model, we also reveal novel drug targets. This article summarizes the theoretical basis underlying the model, the effects of current antipsychotic drugs and the strategy adopted for novel target identification.

Prefrontal cortex deficits in schizophrenia

There is a large body of evidence implicating deficits in prefrontal cortex function in schizophrenia. Functional neuroimaging studies show that patients exhibit reduced glucose utilization and blood flow in the prefrontal cortex (hypofrontality). Although this is often apparent under resting conditions, it is typically exacerbated under a cognitive challenge. For example, hypofrontality has been shown to correlate with working memory deficits as well as executive function deficits in the Wisconsin Card sorting test (Buchsbaum *et al*., 1990; Andreasen *et al*., 1992; Tamminga *et al*., 1992; Volz *et al*., 1999; Hazlett *et al*., 2000; Ragland *et al*., 2007). Hypofrontality has also been implicated in other psychiatric diseases, raising the possibility that there may be some common pathophysiological mechanisms underlying cognitive deficits in disorders such as major depression and drug addiction.

There are, however, fewer studies in depression and drug addiction than in schizophrenia, and although several neuroimaging studies report hypofrontality in depressed patients, the relationship between this and cognitive performance appears to be distinct from that in schizophrenia (Berman *et al*., 1993; Rogers *et al*., 2004; Harvey *et al*., 2005).

Despite the large literature on hypofrontality in schizophrenia, the neuronal mechanisms underlying this pathophysiological feature remain unknown; possible causes include impaired synaptic connectivity and neurotransmission resulting from neurodevelopmental and/or genetic factors. These impairments could explain, at least in part, the dysregulation of dopaminergic activity in the limbic striatum and mediodorsal thalamus, which have reciprocal connections with the prefrontal cortex (corticolimbothalamic circuit). Activity in this corticolimbothalamic circuit is strongly regulated by GABAergic interneurones (chandelier and basket cells), which synapse onto the glutamatergic pyramidal neurones in the prefrontal cortex. These GABAergic interneurones express high concentrations of *N*-methyl-D-aspartate (NMDA) receptors, which have been shown to regulate their excitability. The output of the pyramidal neurones is strongly influenced by the chandelier cells, which are activated by recurrent collaterals from the pyramidal cells. Recurrent activation of these GABAergic inhibitory cells provides a powerful means of feedback inhibition of the pyramidal cells, as the synaptic connection occurs at the axon hillock (Zhu *et al*., 2004). The parvalbumin-containing GABAergic interneurones are proving of particular interest in schizophrenia, as markers of these neurones, the calcium-binding protein parvalbumin, the GABA synthetic enzyme GAD67 and the GABA transporter are reduced in post-mortem brain. Changes have been identified at both the mRNA and protein level, which may indicate reduced activity (Lewis, 2000; Beasley *et al*., 2002). From a preclinical physiological perspective, the parvalbumin-containing GABAergic interneurones express Kv3.1 and Kv3.2 channels potassium, which confer these neurones with fast spiking activity (Kawaguchi and Kondo, 2002) and contribute to their participation in synchronous oscillatory network activity (Rudy and McBain, 2001; Kawaguchi and Kondo, 2002). Furthermore this network activity appears to be related to EEG gamma rhythms and cognitive processing. Indeed, schizophrenia patients exhibit deficits in gamma rhythms (Cho *et al*., 2006), raising the possibility that dysfunction of GABAergic neurones (particularly the parvalbumin-containing cells) is an important contributor to prefrontal cortex dysfunction in the disease.

Can prefrontal cortex deficits be mirrored in preclinical models?

Conventional models of schizophrenia have tended to focus on cellular and behavioural manipulations of dopamine, as the dopaminergic system has been strongly implicated in the disease. However, typical and atypical antipsychotic drugs with D2 receptor antagonist properties that display activity in these models tend to have clinical efficacy limited to the positive symptoms of the disease. Hence, there is a need for improved models to enable the identification of new treatments. A variety of newer animal models are emerging, which include genetic, neurodevelopmental and pharmacological models (see Lipska, 2004; Morris *et al*., 2005; Arguello and Gogos, 2006; Enomoto *et al*., 2007). The validity and future success of these models will reside in their ability to detect new treatments that can treat the disease more effectively than the current antipsychotic drugs.

To date, relatively few models have focussed on prefrontal cortex pathophysiology and resultant behaviours. One neurodevelopmental model (see Lipska, 2004) has shown that the prefrontal cortex is compromised in rats with neonatal ventral hippocampal lesions. Abnormal interactions between dopamine, GABA and glutamate in cortical circuitry in this model are evidenced by alterations in GABA neurone markers such as the GABA synthetic enzyme GAD67, reduced cortical levels of *N*-acetylaspartate and the glutamate transporter EAAC1 and by altered firing patterns of cortical pyramidal neurones in response to dopaminergic nerve stimulation via the ventral tegmental area.

Other groups have focussed on pharmacological models, in particular NMDA receptor hypofunction. This is based on the knowledge that NMDA receptor antagonists such as phencyclidine (PCP) and ketamine exacerbate psychosis in schizophrenic patients and produce positive and negative symptoms as well as cognitive deficits in normal subjects (Javitt and Zukin, 1991; Krystal *et al*., 1994; Malhotra *et al*.,

1996). There are several interrelated hypotheses of NMDA receptor antagonist models (see Jentsch and Roth, 1999; Morris *et al*., 2005; Large, 2007), including reduced activity of neurones containing NMDA receptors, increased glutamate transmission at non-NMDA receptors and impaired inhibitory control in specific cortical circuits. All of these effects could be anticipated after acute NMDA receptor antagonist treatment.

The concept of NMDA receptor hypofunction is in apparent contradiction to the profound increases in cortical excitatory activity after NMDA receptor blockade. An explanation of this phenomenon has stemmed from recent *in vivo* studies, which have shown that NMDA antagonist-induced excitation of glutamatergic pyramidal cells is due to decreased activity of GABA interneurones through blockade of NMDA receptors present in high concentrations on these cells (Homayoun and Moghaddam, 2007). The authors note that the time course of these effects suggests that complex network dynamics are influencing the firing rate of interneurones over a sustained time period.

The acute NMDA receptor antagonist model is attractive in that there are alterations in glutamate receptor subtypes possibly mediated through polymorphisms in NMDA receptor subunit genes (for example, Zhao *et al*., 2006a) in schizophrenia together with deficits in cellular markers of GABA interneurones (Lewis *et al*., 2005). However, in opposition to the 'hypofrontality' of schizophrenia, acute NMDA receptor blockade produces hyperfrontality, that is, increases in glucose utilization and blood flow in the prefrontal cortex (Weissman *et al*., 1987; Gao *et al*., 1993; Duncan *et al*., 1998). Increases in glucose utilization are, in general, paralleled by increases in blood flow and are considered to be a result of enhanced excitatory processing in the brain. This hyperfrontality is in keeping with the results of Homayoun and Moghaddam (2007), who demonstrated NMDA antagonist-induced excitation of glutamatergic pyramidal cells after acute drug treatment.

To increase the face-and-construct validity of an NMDA receptor antagonist model, we have therefore sought to develop a model in which both hypofrontality and GABAergic deficits were present. Notably, adult individuals that abuse PCP/ketamine repeatedly, rather than acutely, display hypofrontality in functional imaging studies (Jentsch and Roth, 1999). Furthermore, the symptoms related to schizophrenia are more severe and enduring than after acute treatment. This suggests a dissociation of the acute and chronic effects of NMDA receptor antagonism on brain mechanisms particularly in relation to prefrontal cortex activity and cognitive deficits. We hypothesized that repeated treatment with NMDA receptor antagonists to adult rodents would evoke neuroadaptive processes more relevant to schizophrenia than acute treatment and that these processes would be manifest as hypofrontality. Our strategy was to assess the effect of repeated low-dose PCP to adult rats (2.6 mg kg^{-1} i.p. daily for 5 days) and assess hypofrontality 72 h after the last treatment, using quantitative ^{14}C- 2-deoxyglucose imaging, which parallels the fluordeoxyglucose imaging technique in human studies for assessing rates of cerebral glucose utilization. Alongside this functional imaging measure, we evaluated parvalbumin

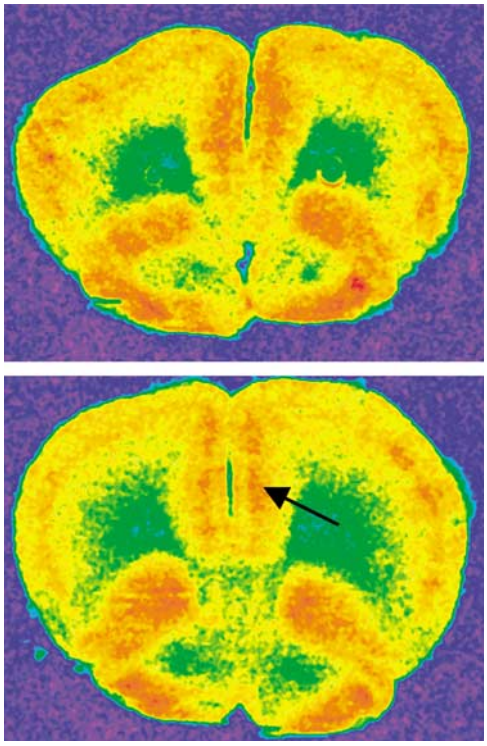

Figure 1 Hypofrontality induced by chronic PCP treatment. Representative autoradiograms showing reduced glucose utilization in the rat prefrontal cortex (hypofrontality) after chronic intermittent PCP (2.6 mg kg^{-1} i.p. for 28 days). Top section: vehicle control; bottom section: chronic PCP treatment (reprinted from permission from Cochran *et al*., 2003a). Arrow denotes reduced glucose use in prelimbic region of the prefrontal cortex.

mRNA expression as a marker of GABA interneurone activity. Although the majority of brain regions showed no change in glucose utilization, repeated PCP treatment led to hypofrontality (decreased glucose utilization in the prefrontal cortex) (Figure 1) together with decreased activity in the reticular thalamus and auditory structures (Cochran *et al*., 2003a). These regionally specific changes were maintained after chronic intermittent treatment with the same dose of PCP for a further 3 weeks (Cochran *et al*., 2003a), suggesting that the changes were restricted to particular corticothalamic circuits. Importantly, this dosing regime also produced reductions in parvalbumin mRNA expression in the PFC and the reticular thalamus. These changes appeared to be restricted to parvalbumin-containing GABAergic interneurones (chandelier and basket cells), as mRNA expression of calcium-binding proteins (calbindin and calretinin) in other classes of interneurones was unchanged. To further substantiate the relevance of parvalbumin-containing subsets of interneurones to our findings, we assessed the expression of a subunit of the Kv3.1 voltage-gated potassium channel after the 5-day and chronic intermittent PCP treatment regime (2.6 mg kg^{-1}). As noted above, these channels are thought to confer fast spiking properties on parvalbumin interneurones (Rudy and McBain, 2001; Kawaguchi and Kondo, 2002). Intriguingly, the reductions in parvalbumin expression 72 h after five daily doses of PCP (2.6 mg kg^{-1}) were paralleled by reductions in Kv3.1 mRNA

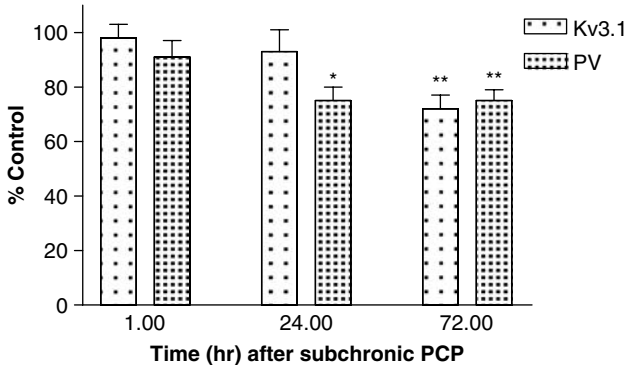

Figure 2 GABAergic interneurone marker deficits following repeated PCP to rats (5 daily doses of 2.58 mg kg^{-1} i.p.) treatment. Kv3.1 and parvalbumin (PV) mRNA expression were assessed using *in situ* hybridization 1.0, 24.00 and 72.00 h after the last dose of PCP. Data are presented as percentage of control means ± s.e.mean. $^{*}P<0.05$, $^{**}P<0.001$, compared to control.

expression, and neither were changed 1 h post-treatment (Figure 2; Cochran *et al*., 2003b). Taken together, these findings add weight to the view that neuroadaptive processes in GABAergic interneurones of the parvalbumin-containing subtypes (chandelier and basket cell) relevant to schizophrenia occur after repeated PCP treatment. An alternative explanation is that the reduced expression of parvalbumin and Kv3.1 mRNA expression is a result of cell death. However, we observed no deficits in markers of cell death with this dosing regime. Furthermore, the reduced expression was reflected as reduced silver grains per cell rather than cell loss (Cochran *et al*., 2003a) and was reversed by clozapine (see below).

These observations may not reflect the results from all studies with NMDA receptor antagonists. Notably the increases in glutamate release from excitatory pyramidal cells after acute NMDA blockade (Homayoun and Moghaddam, 2007) could potentially attain excitotoxic concentrations after high doses of these drugs. Indeed, Olney *et al*. (1989) report widespread cell death following large doses of NMDA receptor antagonists administered to adult rats and Wang and Johnson (2005) have shown that postnatal administration of these drugs produces neurotoxicity. Hence, NMDA receptor antagonists do not represent a single model of schizophrenia; rather the phenotype will depend on the dose of the drug, the duration of the dosing regime as well as when the drug was administered during development. Indeed, the differing effects of NMDA receptor antagonist regimes upon NMDA and AMPA receptor binding and subunit expression and GABA mechanisms (Cochran *et al*., 2002; Rujescu *et al*., 2006; Anastasio and Johnson, 2007; Barbon *et al*., 2007; Newell *et al*., 2007; Wang *et al*., 2007) concur with this idea.

As schizophrenia is not usually regarded as a neurodegenerative disease, concentrations of the NMDA receptor antagonist drug that do not cause widespread excitotoxicity may be predicted to have greater face validity in modelling the schizophrenia phenotype.

In summary, the low-dose chronic PCP model developed in our laboratories produces a hypofrontality and reductions in expression of markers of GABAergic interneurones similar to that observed in schizophrenia. Although the decreases in glucose utilization may not be caused by precisely the same mechanisms as that observed in schizophrenia, the neuroadaptive synaptic changes in brain circuits elicited by this treatment bears the hallmarks of similar dysfunction of corticolimbothalamic circuitry as in schizophrenia.

Hypofrontality is associated with deficits in executive function in schizophrenia, and we were therefore interested in assessing whether such deficits were demonstrable in our model. Patients with schizophrenia exhibit deficits in a variety of cognitive domains including prefrontal cortex-dependent executive function deficits in working memory and set-shifting. In particular, there are deficits in the extradimensional shift discrimination of the Wisconsin Card Sorting Task in first-episode patients, suggesting that this is a core feature of the disease (Joyce *et al*., 2002). We have employed a rodent analogue of this test, the attentional set-shifting task, and demonstrated that repeated (5 daily doses of 2.6 mg kg^{-1} PCP) and chronic intermittent PCP (2.6 mg kg^{-1}) treatment produce deficits in the extradimensional shift similar to those observed in schizophrenia (Egerton *et al*., 2005, 2008). Thus, not only do these treatment regimes produce hypofrontality and GABAergic deficits, but they also produce prefrontal cortex deficits paralleling those observed in patients. Taken together, these results substantiate the view that this is likely to be a valuable translational model of prefrontal cortex deficits in schizophrenia.

Do antipsychotic drugs reverse hypofrontality and GABAergic deficits?

We have assessed the ability of chronic clozapine (20 mg kg^{-1} day^{-1}) and haloperidol (1 mg kg^{-1} day^{-1}) to reverse the chronic PCP-induced deficits in hypofrontality and the GABAergic chandelier and basket cell marker parvalbumin. These dosing regimes reflect plasma concentrations of the drug achieved in the clinic. Importantly, neither drug reversed hypofrontality (Cochran *et al*., 2003a), mirroring the lack of ability of current antipsychotic drugs including clozapine to restore dorsolateral prefrontal cortex 'hypofrontality' in the clinic (Snitz *et al*., 2005; Zhao *et al*., 2006b). Interestingly, chronic clozapine, but not chronic haloperidol, restored parvalbumin deficits in the prefrontal cortex, suggesting some ability to alter GABAergic neurone marker activity in the prefrontal cortex (Cochran *et al*., 2003a). However, these data also suggest that restoration of GABAergic interneurone activity may not be sufficient to restore hypofrontality. To substantiate this view, studies of the chronic PCP regime and electrophysiological measures of GABA interneurone excitability would be of interest.

In summary, we predict that a drug that restores GABAergic deficits and that reverses hypofrontality would offer significant advances over clozapine in the treatment of negative symptoms and cognitive deficits in schizophrenia.

Global transcriptome screen of chronic PCP model

Using our chronic intermittent PCP treatment regime, we have used Affymetric microarray technology to identify

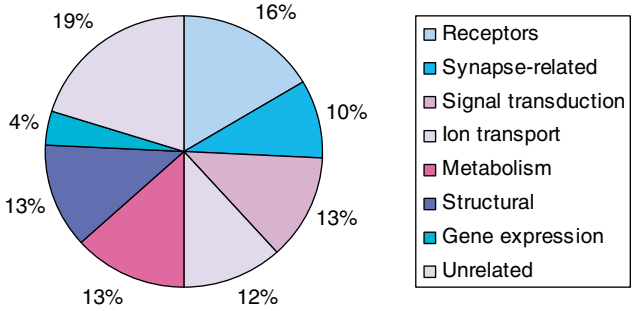

Figure 3 Transcriptome analysis of prefrontal cortex tissue following chronic intermittent PCP treatment. Note that the gene expression changes are consistent with current theories of prefrontal cortex dysfunction in schizophrenia and suggest a multifactorial neurobiological basis of the disease.

novel psychosis-inducing genes associated with prefrontal cortex dysfunction, to dissect pathways involved in the pathophysiology of schizophrenia and to identify novel drug targets incorporating the genetic basis of the disease. Following chronic intermittent PCP treatment to rats, 327 probe sets were differentially expressed in the prefrontal cortex. Data mining and gene ontology revealed that over 50% of these gene expression changes were related to synapse-related genes, receptors (including GABA and glutamate receptors), signal transduction genes and ion channels. This is consistent with current theories of prefrontal cortex dysfunction in schizophrenia (Figure 3) (Winchester *et al*., 2007). Moreover, ~20% of these genes were located on well-replicated chromosomal loci linked to schizophrenia. These included chromosomal loci such as 8p22-21, in which neuregulin 1 (*NRG1*) is located, and 5q33, which have robustly been associated with schizophrenia (Harrison and Weinberger, 2005).

Furthermore, we have identified a novel dysfunctional pathway that is disrupted after chronic PCP treatment that may be highly relevant to schizophrenia. Thus, the products of the differentially expressed genes may form the basis for the development of new therapies by targeting components of known and novel pathways to address glutamate and GABAergic dysfunction.

Conclusion

We have developed a chronic rat PCP model that mirrors the core neurobiological deficits in schizophrenia; hypofrontality, altered GABAergic interneurone activity and extradimensional shift deficits related to executive function. These deficits have been assessed using techniques directly analogous to those used in patients, namely 2-deoxyglucose imaging for assessing glucose utilization similar to fluordeoxyglucose PET imaging in patients, attentional set-shifting analogous to the Wisconsin card sorting task of executive function in humans and mRNA measurements of GABAergic cell markers. We conclude that this model will be a valuable translational model for understanding the neurobiological mechanisms underlying hypofrontality and for identifying and validating novel drug targets that may restore prefrontal cortex deficits in schizophrenia. Indeed, a global transcriptome screen of the model has revealed novel targets that are being taken forward as potential new therapies for the treatment of this debilitating disease.

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Conflict of interest

The authors state no conflict of interest.

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