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***Abstract*:** Schizophrenia is a complex mental health disorder with positive, negative and cognitive symptom domains. Approximately one third of patients are resistant to currently available medication. New therapeutic targets and a better understanding of the basic biological processes that drive pathogenesis are needed in order to develop therapies that will improve quality of life for these patients. Several drugs that act on neurotransmitter systems in the brain have been suggested to model aspects of schizophrenia in animals and in man. In this paper, we selectively review findings from dopaminergic, glutamatergic, serotonergic, cannabinoid, GABA, cholinergic and kappa opioid pharmacological drug models to evaluate their similarity to schizophrenia. Understanding the interactions between these different neurotransmitter systems and their relationship with symptoms will be an important step towards building a coherent hypothesis for the pathogenesis of schizophrenia.

Keywords: amphetamine, cannabis, drug models, kappa opioid, ketamine, LSD, models, PCP, psilocybin, psychosis, salvia divinorum, schizophrenia, THC

Introduction

Existing antipsychotic medications have their main therapeutic effect through dopamine D2 receptor blockade [Kapur and Mamo, 2003]. Although approximately 30% of patients respond to antipsychotic treatment and enter full remission, and a further 30% show some response, around 20–30% do not respond to these medications at all [Meltzer, 1997; Mosolov *et al.* 2012], perhaps due to them having a different neuropathological basis to their condition [Stone *et al.* 2010; Egerton *et al.* 2012; Demjaha *et al.* 2012]. With the exception of clozapine, current antipsychotic medications do not show significant differences in efficacy, and are primarily differentiated by their side-effect profiles [Meltzer, 1997; Abbott, 2010; Lieberman *et al.* 2005]. Side effects can be severe, with extrapyramidal symptoms being typically problematic in typical antipsychotic drugs, and metabolic changes, leading to weight gain and type 2 diabetes, commonly occurring with atypical antipsychotic drugs [Lieberman *et al.* 2005; Langer and Halldin, 2002]. For those patients that do respond, long-term compliance is required, with attempts to discontinue medication generally leading to relapse [Langer and Halldin, 2002; Boonstra *et al.* 2011; Stefansson *et al.* 2008; Pratt *et al.* 2012]. In addition, even when effective in reducing positive symptoms, dopamine-blocking antipsychotic drugs are largely ineffective at reducing negative symptoms and cognitive impairments, and it is these domains that are the most important predictors for long-term social functioning [Langer and Halldin, 2002; Stefansson *et al.* 2008; Pratt *et al.* 2012]. There is thus a pressing need to develop novel treatments that have more tolerable side effects, and that are effective in those patients who fail to respond to currently available antipsychotic drugs. Drug models of psychosis may assist in the identification of alternative therapeutic targets and may be utilized in the development and screening of novel compounds prior to testing in patients.

The ideal model of schizophrenia would faithfully mimic the biological changes driving pathogenesis and carry high predictive value for the efficacy of novel therapeutics [Langer and Halldin, 2002]. Many drug models of schizophrenia have been investigated for this purpose, and several have shown promising results. It is important to note that, in contrast to drug models, schizophrenia is chronic, neurodevelopmental, and episodic with different symptom domains predominating at different stages.

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Therefore, any purely pharmacological model is likely destined to be incomplete in the extent to which it can represent the full picture of schizophrenia.

Common discrepancies between pharmacological models and schizophrenia include an inability to faithfully mimic all of the symptom domains, insight into the fact that the symptoms were caused by a drug, and the experience of euphoria, or simply of liking the drug effects [Curran *et al.* 2009; Abi-Saab *et al.* 1998]. Furthermore, some drugs known to induce schizophrenia-like symptoms in humans do so only after continued administration (e.g. amphetamine), which make them less suitable for experimental medicine studies due to ethical concerns as well as issues with practicality and the increased risk of adverse effects. In testing novel antipsychotics against drug models of psychosis, it is also worth considering that any observed attenuation of symptoms with the antipsychotic may be due to a pharmacological interaction that is irrelevant to the biology of schizophrenia [Jones *et al.* 2011].

Animal models of psychosis have some advantages for testing novel agents, as chronic and perinatal dosing regimens are possible, but they are difficult to interpret unless they have been extensively cross-validated with human models. All of the primary symptoms of schizophrenia, such as hallucinations, delusions and thought disorder, require verbal report for their measurement in order to be properly tested and measured, and it is not always clear how relevant animal-based biomarkers are to the uniquely human symptoms of schizophrenia. Furthermore, putative therapeutic agents do not always have the same effects in animals as in man [Pratt *et al.* 2012; Curran *et al.* 2009; Jones *et al.* 2011].

Several drugs induce effects that resemble at least some of the symptoms of schizophrenia in animals and man [Curran *et al.* 2009; Jones *et al.* 2011; Marcotte *et al.* 2001]. In this review, we investigate the relative strengths of dopaminergic, glutamatergic, serotonergic, endocannabinoid, GABAergic, cholinergic and kappa-opioid pharmacological models of schizophrenia, comparing neurochemical findings in schizophrenia supporting the models, considering the effects of the candidate drugs in humans and contrasting evidence from animal models.

Pharmacological models of schizophrenia

Dopaminergic

The relationship between the clinical effective dose of antipsychotic drugs and their affinity for the D2 receptor has been established for more than 30 years [Seeman and Lee, 1975; Kapur *et al.* 2005]. Patients with schizophrenia have been shown to have evidence of abnormal dopaminergic function, with increased dopamine release following amphetamine administration, elevated synaptic dopamine and increased [18F] DOPA uptake [Laruelle *et al.* 1996, 2003; Kegeles *et al.* 2002, 2010; Abi-Dargham *et al.* 2009; Howes *et al.* 2012]. The dopaminergic theory of aberrant salience provides an explanation for some of the positive delusional symptoms of psychosis due to overactive mesolimbic dopaminergic transmission [Kapur *et al.* 2005; Seeman, 1987; Seeman and Kapur, 2000]. In contrast, it has been suggested that an underactive dopamine system in the frontal cortex may underlie some of the negative symptoms [Davis *et al.* 1991].

The psychostimulants amphetamine and cocaine increase synaptic levels of dopamine, and have been reported to exacerbate psychotic episodes in people with existing schizophrenia [Farren *et al.* 2000; Bramness *et al.* 2012]. In early studies of amphetamine administration in healthy volunteers, large single oral doses were found to induce an acute psychosis [Angrist and Gershon, 1970; Bell, 1973]. However, at lower doses, paranoid and other psychotic symptoms emerge only with repeated dosing, and only in some individuals. It has been suggested that amphetamines may act as a stressor to induce psychosis in a vulnerable subset of the population [Bramness *et al.* 2012].

Positive symptoms induced by amphetamines and cocaine include auditory hallucinations, thought disorder and grandiose delusions, and chronic amphetamine users have been found to score highly on the Positive and Negative Syndrome Scale (PANSS) [Angrist and Gershon, 1970; Harris and Batki, 2000; Wolkin *et al.* 1994; Angrist *et al.* 1974]. However, in a recent survey of effects associated with amphetamine use, we found that schizophrenia-like effects were relatively rare in regular users, and that experienced users ranked amphetamine behind ketamine and alcohol in terms of its propensity to cause thought disorder, and behind cannabis, psilocybin and ketamine in terms of likelihood of inducing

hallucinations and delusions [Carhart-Harris *et al.* 2013a].

In rodents, administration of dopaminergic stimulants has been reported to induce repeated ('stereotyped') behaviours, such as locomotion, sniffing and chewing, that may be related to the positive symptoms of psychosis, as well as to impaired prepulse inhibition (PPI), a marker of sensory gating impairment also seen in patients with schizophrenia [Segal and Mandell, 1974]. With chronic dosing, the PPI and stereotyped behaviours occur at increasing frequency and duration over time [Segal and Mandell, 1974]. This phenomenon is termed 'sensitization' and some groups have suggested that sensitization shares common mechanisms with the development of psychosis in man [Ujike, 2002; Featherstone *et al.* 2007]. This induced state has been linked to: (1) changes in the inhibitory dopamine D3 receptor function (possibly by down-regulating their availability for stimulation); (2) altered dopamine transmission in the nucleus accumbens; and (3) increases in total D2 receptor dimerization [Wang *et al.* 2010; Richtand *et al.* 2001]. As in patients with schizophrenia, sensitized rats show an enhanced dopamine release in response to amphetamine compared with controls, and some limited but long-term cognitive impairments have also been reported in attention and set-shifting which are features of schizophrenia [Tenn *et al.* 2003; Fletcher *et al.* 2005]. Amphetamine-induced sensitization is commonly used as a model for the positive symptoms of schizophrenia but it is not thought to fully resemble the cognitive and negative symptom domains [Jones *et al.* 2011; Wang *et al.* 2010]. Furthermore, purely dopaminergic models are likely to lead to the development of more dopamine-targeting antipsychotic drugs, which may be unlikely to lead to a great improvement in efficacy or safety. Thus, alternative models are of interest for the identification of novel drug targets.

Glutamatergic

The NMDA receptor hypofunction hypothesis of schizophrenia has been suggested as an alternative or additional neurochemical model of schizophrenia to the dopamine hypothesis [Olney and Farber, 1995; Goff and Coyle, 2001]. Glutamate signalling plays an important role in synaptic plasticity and cortical processing in the brain and genetic studies have implicated abnormalities in this system as possible drivers of pathogenesis in schizophrenia [Schwartz *et al.* 2012]. It has also been suggested that glutamate-driven excitotoxicity could underlie reductions in grey matter volume seen in schizophrenia [Olney and Farber, 1995; Okugawa *et al.* 2007; Hertzmann *et al.* 1990]. Although there is little direct evidence of NMDA receptor hypofunction in schizophrenia, one imaging study using an NMDA receptor single photon emission tomography tracer reported a reduction in NMDA receptor binding in medication free patients with schizophrenia [Pilowsky *et al.* 2006]. Similarly, NMDA receptor NR1 subunit mRNA has been reported to be reduced in post-mortem patients with schizophrenia [Law and Deakin, 2001].

The dissociative anaesthetics phencyclidine (PCP) and ketamine are both uncompetitive NMDA receptor antagonists suggested to be pharmacological models of schizophrenia [Laruelle *et al.* 2000]. They have been shown to lead to increases in the power of gamma oscillations [Rotaru *et al.* 2012], increases in functional connectivity [Driesen *et al.* 2013], and increases in prefrontal glutamate (or glutamine) levels, demonstrated both in animal microdialysis studies, and in human proton magnetic resonance spectroscopy (^{1}H-MRS) studies [Moghaddam *et al.* 1997; Rowland *et al.* 2005; Stone *et al.* 2012a]. The mechanism by which they lead to these changes is still controversial, although it has been shown that NMDA receptor inhibition leads to a reduction in GABAergic interneuron function, possibly through preferential effects of ketamine on NMDA receptors expressed on these cells [Homayoun and Moghaddam, 2007]. This has been suggested to lead to increases in pyramidal cell firing due to disinhibition [Olney and Farber, 1995]. Recent work suggests that the preferential blockade of NMDA receptors on cortical GABAergic interneurons is unlikely to occur, however, with more evidence for a preferential sensitivity of pyramidal cell NMDA receptors to ketamine [Rotaru *et al.* 2012]. One intriguing possibility is that reductions in GABAergic interneuron function may be mediated by the generation of brain superoxide, since inhibiting superoxide levels prevented reductions in interneuron activity following ketamine administration [Behrens *et al.* 2007]. Furthermore, inhibition of the formation of reactive oxygen species prevents the psychosis-like effects of NMDA receptor blockade in animal models [Sorce *et al.* 2010; Levkovitz *et al.* 2007; Zhang *et al.* 2007; Monte *et al.* 2013].

Ketamine has been demonstrated to exacerbate positive and negative symptoms in pre-existing schizophrenia [Lahti *et al.* 1995b] and, in some patients, use has been linked to impairment in cognition, specifically by inducing a larger deficit in recall memory in people with schizophrenia compared to controls [Malhotra *et al.* 1997; Lahti *et al.* 1995a]. Acute doses of ketamine in healthy volunteers induce schizophrenic-like positive and negative symptoms, and may also lead to impairments in cognitive function that resemble schizophrenia [Stone *et al.* 2012a; Krystal *et al.* 2005; Morgan *et al.* 2004; Deakin *et al.* 2008]. Ketamine binding to NMDA receptors has been reported to correlate with its effect on negative symptoms [Stone *et al.* 2008] whereas downstream effects of ketamine, including increases in ^{1}H-MRS-measured prefrontal glutamate levels and ketamine-induced changes in functional magnetic resonance imaging (fMRI) signal, correlated with ratings of positive psychotic symptoms [Stone *et al.* 2012a; Deakin *et al.* 2008], suggesting that different symptom clusters may have distinct underlying mechanisms.

There are several dissimilarities between the ketamine-induced state and schizophrenia [Steen *et al.* 2006]. For example, auditory hallucinations are one of the most common symptoms in schizophrenia, but the hallucinations and illusions experienced following acute administration of ketamine are more commonly visual [Abi-Saab *et al.* 1998; Steen *et al.* 2006]. On this basis, it has been suggested that, rather than modelling chronic schizophrenia, acute ketamine administration may induce a state closer to the prodrome/early stages of schizophrenia, when fleeting visual changes of the type that occur following ketamine administration have also been reported to occur [Klosterkotter *et al.* 2001; Corlett *et al.* 2007].

Another criticism of acute ketamine or PCP administration is that it is unlikely to be able to replicate the neurobiological changes that occur over time in the schizophrenic brain [Malhotra *et al.* 1997; Tsai and Coyle, 2002]. Thus, there has been considerable interest in the long-term effects of these drugs. Some chronic PCP and ketamine users have been found to have persistent schizophrenia-like symptoms [Jentsch and Roth, 1999; Krystal *et al.* 1994], and such patients may present with a symptomatic profile that can so closely resemble schizophrenia that it may even be misdiagnosed as such [Abi-Saab *et al.* 1998; Javitt, 1987]. Reported symptoms in chronic PCP and ketamine users may include paranoid delusions, persistent cognitive deficits and, in chronic PCP users, there have been reports of a greater incidence of auditory than visual hallucinations [Jentsch and Roth, 1999]. Depressive and dissociative symptoms also increase with persistent use of ketamine in chronic users [Morgan *et al.* 2004].

Biochemical brain changes that are similar to those seen in patients with schizophrenia have been found in chronic ketamine and PCP users. Dopamine D1 receptors are upregulated in the frontal cortex of patient with schizophrenia and in chronic ketamine users [Narendran *et al.* 2005]. This upregulation is associated with cognitive impairment and dopaminergic hypofunction [Narendran *et al.* 2005]. Chronic ketamine users have also been found to have other brain imaging changes associated with schizophrenia including reduced thalamic NAA [Stone *et al.* 2014b], and reduced prefrontal grey matter volume [Liao *et al.* 2011]. Furthermore, chronic PCP users have been found to have decreased blood flow in the frontal cortex, similar to that seen in schizophrenia [Hertzmann *et al.* 1990].

In animal models, NMDA receptor antagonists induce behavioural, locomotor and cognitive changes, and chronic administration also induces neurobiological changes similar to those found in the brains of schizophrenia patients [Jones *et al.* 2011; Jentsch and Roth, 1999]. Primates given a chronic infusion of PCP display scanning and pacing behaviours and rodents develop deficits in motor planning, working memory and stereotypies [Linn *et al.* 1999]. These symptoms can be attenuated, but not abolished completely, with antipsychotic medication, which may suggest something of their underlying neurobiology [Steinpreis *et al.* 1994]. Importantly, chronic administration of PCP may be a useful means to study similar degeneration to that seen in the brains of schizophrenia patients because it also induces cortical neurodegenerative changes in rats [Olney and Farber, 1995; Wang and Johnson, 2005]. This effect can be blocked by AMPA receptor antagonists and so it may be that excess glutamate release is driving neurotoxicity in the model [Olney and Farber, 1995; Deutsch *et al.* 2001]. In rodents with chronic PCP treatment, PPI is disrupted, dopaminergic transmission in the frontal lobe is reduced and changes in the mesolimbic and frontal–cortical dopamine systems mimic those of schizophrenia [Jones *et al.* 2011; Jentsch and Roth, 1999]. Chronic neonatal

administration of PCP induces lasting cognitive deficits and increases in putative animal equivalents of positive symptoms [Stefani and Moghaddam, 2005; Uehara *et al.* 2010]. Furthermore, in primate models, these neurobiological changes persist beyond the acute effects of the drug and behavioural and cognitive deficits can still be seen after PCP administration has been stopped [Olney and Farber, 1995; Jentsch *et al.* 1997].

The models generated by the use of dissociative anaesthetics demonstrate that NMDA receptor dysfunction could be a key factor in the pathogenesis of schizophrenia [Olney and Farber, 1995; Laruelle *et al.* 2000; Javitt and Zukin, 1991]. NMDA receptor antagonist models of schizophrenia could have value in predicting the efficacy of much needed therapies that target the cognitive and negative symptom domains of the illness because of their evident interaction with areas of cognition relevant to schizophrenia [Laruelle *et al.* 2000; Neill *et al.* 2010]. It should be borne in mind, however, that these drugs are known to act on multiple neurotransmitter systems in the brain including dopamine [Jentsch *et al.* 1997; Kapur and Seeman, 2002], and this may be central to their generation of a more complete clinically picture of schizophrenia than those that act primarily on a single neurotransmitter system.

Serotonergic

Although less widely studied than dopamine or glutamate, there is evidence that the serotonin (5-HT) system may also be involved in psychotic symptom formation. Support comes from the observation that hallucinogens such as LSD and psilocybin are 5-HT_{2A} receptor agonists [Vollenweider and Geyer, 2001]. These drugs induce psychopathologies which include agitation, anxiety, visual hallucinations and illusions, which are similar to symptoms seen in the first psychotic episode of the illness [Fletcher and Honey, 2006; Hyde *et al.* 1978]. Furthermore, these drugs disrupt PPI through direct stimulation of the 5-HT_{2A} receptors [Quednow *et al.* 2012; Aghajanian and Marek, 2000], lead to a blending of the brain networks engaged during rest and active task performance [Carhart-Harris *et al.* 2013b], and lead to downstream increases in glutamate release [Scruggs *et al.* 2003; Muschamp *et al.* 2004], closely resembling effects seen in patients with psychosis. It is interesting to note that blockade of 5-HT_{2A} receptors inhibits the effects of NMDA receptor antagonists, suggesting that at least some of the psychosis-like effects of NMDA receptor antagonism may be mediated via serotonergic mechanisms [Aghajanian and Marek, 2000; Breese *et al.* 2002].

Many atypical antipsychotics such as clozapine, risperidone and olanzapine are 5-HT_{2A} receptor antagonists, having higher affinity for 5-HT_{2A} receptors than for dopamine D_2 receptors [Jentsch and Roth, 1999; Williams *et al.* 1997; Meltzer, 1996]. It is unclear to what extent these properties are involved in their antipsychotic effect, however. 5-HT2A receptor antagonists have been suggested to be potentially useful in improving cognition or negative symptoms in patients with schizophrenia [Akhondzadeh *et al.* 2008; Roth *et al.* 2004], but trials of 5-HT2A antagonists for schizophrenia to date have not progressed beyond phase III due to lack of efficacy against positive symptoms [de Paulis, 2001; Ebdrup *et al.* 2011].

There are several differences between the symptoms of schizophrenia and the hallucinogenic state induced by serotonergic drugs [Corlett *et al.* 2009]. With serotonergic drugs, subjects tend to experience hallucinations which are generally visual, and so not typical of established schizophrenia, although they may resemble symptoms that occur in the early phase of psychosis [Klosterkotter *et al.* 2001; Geyer and Vollenweider, 2008]. Perceptions and expectations of the action of these drugs can also alter the subsequent psychedelic experience and this means that the effects of the drugs can be unpredictable for different subjects, possibly making it a model that is difficult to reliably reproduce [Corlett *et al.* 2009]. Nonetheless, schizophrenia-like states can be observed in people while on these drugs and altered activity in the prefrontal cortex results in mild thought disorder and altered perception which are similar to that seen in schizophrenia [Carter *et al.* 2005; Strassman *et al.* 1994; Carhart-Harris *et al.* 2012]. Furthermore, individuals with a family history of schizophrenia appear to be at greater risk of schizophreniform symptoms following LSD [Vardy and Kay, 1983], and it has been suggested that LSD use may lead to an earlier onset of schizophrenia [Breakey *et al.* 1974].

Many studies have shown that humans and rodents can develop tolerance to psychedelics and so this model may be limited in the extent to which it can represent the long-term neurobiological changes that characterize the schizophrenic brain

[Marcotte *et al.* 2001]. However, a recent study has shown that chronic administration of lower doses of LSD in rodents can induce a behavioural syndrome that persists after the drug is stopped [Marona-Lewicka *et al.* 2011]. Symptoms from this chronic administration include irritability, hyper-sensitivity to noise, anhedonia, social withdrawal and locomotor changes, which can be reduced by the administration of antipsychotic drugs [Marona-Lewicka *et al.* 2011].

Endocannabinoid

Manipulation of the endocannabinoid system provides another possible way to model schizophrenic-like symptoms. The primary active component of cannabis, delta-9 tetrahydrocannabinol (THC) is an agonist of the cannabinoid receptor CB_1. Its mechanism of action is not fully understood but binding of this molecule may act downstream of dopamine release and play a regulatory role in several neurotransmitter systems [Kuepper *et al.* 2010; Koethe *et al.* 2009]. The endocannabinoid system plays a role in attention, learning and memory and so dysregulation of this system could plausibly be another contributor to the pathogenesis of schizophrenia [Fernandez-Espejo *et al.* 2009; Solowij and Michie, 2007].

Acute cannabis or THC administration may induce positive and negative symptoms as well as cognitive impairments resembling those of schizophrenia in healthy individuals, and may also exacerbate the symptoms of schizophrenia in those already affected by the condition [Koethe *et al.* 2009; Morrison *et al.* 2009; Morrison and Stone, 2011; D'Souza, 2007; D'Souza *et al.* 2004, 2005; Stone *et al.* 2014a]. Cannabis administration is associated with changes in neurophysiological measures that resemble those seen in patients with schizophrenia including P50 suppression, mismatch negativity and the P300 potential [Gallinat *et al.* 2012]. THC has also been shown to modulate binocular depth perception, in a manner that resembles changes seen in prodromal psychosis and schizophrenia [Koethe *et al.* 2006]. THC-induced psychotic symptoms have been shown to be associated with disruption of coherence between frontal theta brain activity [Morrison *et al.* 2011], and with changes to the normal pattern of brain activity preceding conscious action [Stone *et al.* 2012b; Ford *et al.* 2002, 2007]. Disruptions of brain activity prior to the onset of willed action have also been demonstrated in patients with schizophrenia, and are suggested to underlie impairments in efference copy generation, leading to misrecognition of self-generated actions as arising from an external source [Stone *et al.* 2012b; Ford *et al.* 2002].

Rodent and primate THC models mimic some of the cognitive impairments seen in schizophrenia. For example, a dose-dependent impairment in spatial working memory has been reported in adult rhesus monkeys following THC administration and the effect is more marked when THC is administered in adolescence when the brain is more vulnerable to chemical interference [Verrico *et al.* 2012]. Working memory dysfunction, impaired PPI and persisting behavioural changes with underlying neurobiological changes following adolescent exposure, have been observed in rodents following THC treatment, effects that could be symptomatically controlled with antipsychotic agents given to adult rats [Realini *et al.* 2009; Rubino *et al.* 2008; Schneider and Koch, 2003].

Further support for endocannabinoid models of psychosis comes from research using cannabidiol (CBD). Although it has relatively low affinity for CB1 and CB2 receptors in displacement studies, cannabidiol appears to act as noncompetitive antagonist of both CB1 and CB2 receptors at relatively low concentrations when studied *in vivo*, although the mechanism by which this occurs has still not been fully elucidated [Thomas *et al.* 2007]. CBD has been reported to have anxiolytic and antipsychotic properties, with a recent double-blind placebo-controlled study in patients with early stage schizophrenia reporting efficacy *versus* psychotic symptoms of similar magnitude to existing antipsychotic agents, but with a lower incidence of side effects [Leweke *et al.* 2012]. This suggests that the symptoms of schizophrenia may emerge, at least in part, through activation of CB1 and/or CB2 receptors, and CBD may inhibit this effect. Interestingly, CBD has been reported to reduce the psychomotor activating effects of ketamine, with a trend to reduce ketamine-induced depersonalization [Hallak *et al.* 2011], suggesting that some of the downstream effects of NMDA receptor blockade may be mediated by the endocannabinoid system.

GABAergic

There is a growing body of evidence for the dysfunction of GABAergic neurons in schizophrenia and, as gamma-aminobutyric acid (GABA) signalling interacts very closely with glutamatergic

and dopaminergic, models of GABAergic dysfunction may help to unify our understanding of schizophrenia [Pratt *et al.* 2012]. Post-mortem studies have found differences in GABA receptor subunit expression and reduced GABAergic cell types in the brains of schizophrenic patients [Pratt *et al.* 2012]. It is also known that the GABA system undergoes changes during adolescence and that this is a time where patients commonly begin to show symptoms of schizophrenia [Lewis *et al.* 1999]. Furthermore GABAergic firing regulates dopamine transmission in the prefrontal cortex and a GABA interneuron deficit in schizophrenia has been proposed to underlie some of the clinical symptoms [Lewis *et al.* 1999; Japha and Koch, 1999]. GABA-A antagonists disrupt PPI when injected into the rodent medial prefrontal cortex through their action on the dopaminergic system, an effect which can be reversed with D2-blocking antipsychotic drugs [Japha and Koch, 1999]. In a related theory (arising from the methylazoxymethonol acetate rodent model of schizophrenia), Lodge and Grace hypothesized that increased hippocampal glutamatergic outputs, arising secondary to reductions in hippocampal parvalbumin staining GABAergic interneurons in schizophrenia, drive increased striatal dopamine activity [Lodge and Grace, 2011; Gill *et al.* 2011]. Grace and collaborators subsequently showed that a novel positive allosteric modulator of the alpha-5 subunit of GABA-A receptors reduced hyperactive locomotor response and spontaneously active VTA dopamine neurons in this model [Gill *et al.* 2011], suggesting that normalization of hippocampal GABAergic function might be a valid approach to antipsychotic drug development.

There is some evidence that GABA-A receptor manipulation affects psychotic symptoms on humans. In a recent study, the benzodiazepine receptor antagonist iomazenil led to worsening of psychotic symptoms and perceptual alterations in patients with schizophrenia, but not controls [Ahn *et al.* 2011]. In healthy volunteers, the combination of iomazenil with m-cholorphenylpiperizine (m-CPP), a partial agonist of 5-HT2A/2C receptors, has also been shown to lead to perceptual disturbances and other effects suggested to resemble psychosis [D'Souza *et al.* 2006]. In contrast, the psychoactive component of the fly agaric mushroom, muscimol, is a potent GABA-A receptor agonist, and this, and other, GABA-A agonists have generally been found to lead to confusion in healthy volunteers, and worsening of schizophrenia in patients, possibly through preferential action at presynaptic receptors [Meldrum, 1982; Yamamoto *et al.* 2011].

Although there is considerable interest in the potential for novel drugs targeting GABA neurotransmission in schizophrenia [Rudolph and Knoflach, 2011], results from existing compounds in patients have not been promising [Rudolph and Knoflach, 2011; Buchanan *et al.* 2011]. It is hoped that novel approaches to this system may yield additional benefit [Rudolph and Knoflach, 2011].

Cholinergic

There has been considerable interest in both nicotinic and muscarinic neurotransmission in schizophrenia.

Nicotinic. It is well recognized that patients with schizophrenia have a much higher use of tobacco than other patients with mental illness, and it was hypothesized that this may be in an effort to self-medicate and reduce some of the negative and cognitive symptoms of the illness [Ripoll *et al.* 2004]. Patients with schizophrenia have been reported to have reduced alpha-4 and alpha-7 nicotinic receptor brain expression in post-mortem studies [Ripoll *et al.* 2004], and nicotine has been reported to improve PPI in NMDA receptor antagonist models of psychosis [Domino *et al.* 2004; Levin *et al.* 2005], although nicotine did not attenuate ketamine effects in humans [D'Souza *et al.* 2012]. A number of alpha-7 nicotinic agonists have been developed for use in patients with schizophrenia, and early trials have shown promising results on cognitive and negative symptoms [Lieberman *et al.* 2013; Freedman *et al.* 2008].

Although nicotinic antagonists are generally used as muscle relaxants and are not thought to have any effects on mental state, the centrally acting drug bupropion has some effect on inhibiting nicotinic receptors and has also been reported that it may be associated with the development of psychotic symptoms [Kumar *et al.* 2011]. However, given its rich pharmacology, including actions as a dopamine and noradrenaline reuptake inhibitor [Arias *et al.* 2009], it is questionable whether nicotinic receptor antagonism is involved in this effect. Furthermore, Varenicline, a partial agonist at alpha-4 nicotinic receptors, and a full agonist at alpha-7 nicotinic receptors [Mihalak *et al.* 2006], has been reported to have no significant effect in

worsening psychotic symptoms in patients with schizophrenia, with only 5% of patients reporting an increase in symptoms [Cerimele and Durango, 2012]. It thus seems that nicotinic receptor antagonism does not reliably induce or worsen positive psychotic symptoms, and due to the systemic effects of full nicotinic receptor antagonists, it is unlikely nicotinic antagonists would be useful to model for cognitive impairment in schizophrenia.

Muscarinic. Blockade of acetylcholine receptors with atropine, scopolamine and other drugs have been reported to lead to delirium and hallucinations (generally visual) [Perry and Perry, 1995], as well as cognitive impairments [Minzenberg *et al.* 2004; Klinkenberg and Blokland, 2010], and it has been suggested that antimuscarinic drugs may induce a syndrome closely related to schizophrenia [Barak, 2009].

Unmedicated first episode patients with schizophrenia have been reported to have reduced muscarinic receptor availability [Raedler *et al.* 2003], and clozapine has higher occupancy of muscarinic receptors than olanzapine [Raedler, 2007]. It is possible that this binding may underlie some of clozapine's enhanced efficacy, as has been shown to be an M1/M4 partial agonist, and another drug (xanomeline) sharing this property has been reported to show antipsychotic efficacy *versus* positive and negative symptoms, as well as improvements in measures of cognition in early clinical trials [Mirza *et al.* 2003; Shekhar *et al.* 2008]. Problems with cholinergic side effects from xanolemine have led to high levels of dropout from these studies, however [Mirza *et al.* 2003]. Scopolamine has been used to model cognitive impairments [Klinkenberg and Blokland, 2010], and it seems reasonable that these drug-induced effects may have a similar neurochemical basis to those occurring in schizophrenia, and so could provide a target for the development of novel agents to improve cognition in affected patients [Barak and Weiner, 2011].

Kappa opioids

Salvia divinorum is a kappa opioid agonist, which is becoming more commonly used as a recreational drug, and which leads to potent symptoms of dissociation and complex and vivid hallucinations (visual, tactile and auditory) [Johnson *et al.* 2011; Lange *et al.* 2010; Ranganathan *et al.* 2012]. However, the effects of salvia divinorum may not be particularly representative of schizophrenic psychosis, since participants describe entering other realms and meeting entities or beings [MacLean *et al.* 2013] and this is rarely reported in schizophrenia. Although long-term effects have not generally been reported, there is one case report of an individual developing schizophreniform psychosis following exposure to salvia divinorum [Przekop and Lee, 2009].

There has been some suggestion that kappa opioid receptors may be abnormally distributed in the hippocampus in patients with schizophrenia, and that cerebrospinal fluid (CSF) level of dynorphins, the endogenous peptide ligands for kappa opioid receptors, may correlate with symptomatology and response to antipsychotic treatment [Tejeda *et al.* 2012]. However, research studies into the kappa opioid system in schizophrenia have been relatively small in scale, and further work is required [Tejeda *et al.* 2012].

Convergence of models via prefrontal glutamate

Several of these proposed models, in particular, acute NMDA receptor blockade, $5HT_{2A}$ agonism, THC administration and amphetamine administration, have all been reported to increase synaptic glutamate levels in prefrontal cortex (either measured directly by microdialysis, or estimated using ^{1}H-MRS) [Moghaddam *et al.* 1997; Rowland *et al.* 2005; Stone *et al.* 2012a; Scruggs *et al.* 2003; Muschamp *et al.* 2004; Pistis *et al.* 2002; Del Arco *et al.* 1998]. Although it has not been established whether the increased glutamate levels are associated with the psychosis-like effects of these drugs, it is interesting to note that glutamine, a marker of increased prefrontal glutamate release, has been reported in patients in the early phase of psychosis [Marsman *et al.* 2013] and, furthermore, that prefrontal glutamate levels appear to be associated with failure to achieve remission following dopaminergic antipsychotic drug treatment [Egerton *et al.* 2012; Demjaha *et al.* 2014; Szulc *et al.* 2013].

It should be noted that studies using 1H-MRS are still somewhat conflicting in terms of the metabolites affected in the medial prefrontal cortex – studies investigating response to antipsychotic drugs have generally reported associations with glutamate levels, which may represent a total pool of glutamate (both metabolic and neurotransmitter), whereas early psychosis has been associated with increased glutamine levels in the same brain

region. Furthermore, in one study in healthy volunteers ketamine was reported to increase medial prefrontal glutamine levels acutely [Rowland *et al.* 2005], whereas in a second study, ketamine increased glutamate levels subacutely [Stone *et al.* 2012a]. It is possible that estimated glutamine levels (generated following the release of glutamate as a neurotransmitter) may reflect a higher active turnover of glutamate through neurotransmission, with increased estimated glutamate concentration occurring as a downstream consequence (possibly due to more glutamate being generated secondary to the increased turnover). The only way to study this directly in humans at present is with ^{13}C MRS, which, although a powerful approach, is costly and limited in resolution [Rothman *et al.* 2011; Ramadan *et al.* 2013].

Conclusion

Dopaminergic psychostimulants provide a good model of the paranoid psychosis of schizophrenia but do not accurately mimic the cognitive or negative symptom domains [Pratt *et al.* 2012]. Use of dopaminergic models to predict the efficacy of novel therapeutics is likely to select only the medications that primarily act on dopamine transmission. In contrast, NMDA receptor antagonists and THC both generate a more complete model of schizophrenia, including aspects of the positive, negative and frontal cognitive symptoms [Krystal *et al.* 1994; Morrison *et al.* 2009; Morrison and Stone, 2011; D'Souza *et al.* 2004]. Chronic administration of THC and NMDA receptor antagonists in animal models also induce neurobiological changes similar to those seen in schizophrenia and their action on several overlapping neurotransmitter systems means that these drugs could give more insight into the complex clinical condition.

While much research has been done into the role of dopamine, glutamate and cannabis in schizophrenia, other models may also have value with further investigation. Serotonergic hallucinogens model some aspects of prodromal and first episode psychosis in humans and chronic low doses in animal models seem to be able to mimic more symptom domains [Marona-Lewicka *et al.* 2011]. Furthermore, although drugs affecting GABAergic and cholinergic receptors are less likely to directly induce psychosis-like effects in healthy volunteers, there is a substantial amount of evidence for these neurotransmitter systems being altered in patients with schizophrenia. Drugs targeting GABA and acetylcholine receptors may still prove to be a promising avenue for novel treatments in schizophrenia [Rudolph and Knoflach, 2011; Foster *et al.* 2012].

The development of translational animal models based on findings from human studies is important for the rapid testing of novel antipsychotic agents. Objective measurements for different symptoms have already begun to show promise in being able to predict the therapeutic efficacy of new antipsychotics and could give key insight into the effects of abnormalities in specific brain circuitry in schizophrenia [Curran *et al.* 2009].

While pharmacological models may never be able to accurately mimic all aspects of such a complex condition as schizophrenia, they may still be able to provide valuable insight into the neurobiological mechanisms underlying specific symptom domains [Curran *et al.* 2009]. Targeting individual neurotransmitter systems has highlighted the extent to which these systems interact and understanding these links will be an important step towards building a single coherent hypothesis for the pathogenesis of schizophrenia [Japha and Koch, 1999]. It is hoped that new developments in this field will generate new understanding of the biological underpinnings of schizophrenia and so facilitate the development of improved therapeutics [Abbott, 2010; Curran *et al.* 2009].

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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