PCP: from pharmacology to modelling schizophrenia

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Phencyclidine has attracted the attention of neuroscientists for many years because of its ability to produce, in humans, a range of symptoms remarkably similar to those of patients suffering from schizophrenia. The main action of phencyclidine is as a non-competitive antagonist of the NMDA class of glutamate receptor. In the past few years, dramatic advances have been made in our understanding of the neuroanatomical and pathological basis of schizophrenia. In turn, these have allowed assessment of the ability of phencyclidine to produce equivalent changes in the rodent CNS. It has now become clear that chronic intermittent low doses of phencyclidine produce a pattern of metabolic and neurochemical changes in the rodent brain that mirror those observed in the brains of schizophrenic patients with impressive precision. This should be of enormous benefit in the search for new anti-psychotic drugs with improved efficacy against the full range of schizophrenic symptoms.

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Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionate
GABA	γ-aminobutyric acid
NMDA	N-methyl-D-aspartate
PCP	phencyclidine

Introduction

Phencyclidine (PCP) (Figure 1) was first developed as a surgical anesthetic. Despite its useful efficacy, widespread clinical use was not possible because, after surgery, patients experienced hallucinations, disordered speech, delirium, agitation and disoriented behavior. However, partly because of its relative ease of manufacture, PCP has continued to be used illicitly under a variety of names including 'Angel Dust' and 'Hog'. A closely related drug — ketamine (Figure 1) — has suffered from similar (although less pronounced) problems, but is still used in veterinary and paediatric anaesthesia. PCP is of major interest to neuroscientists because of the remarkably close parallels between the experiences and symptoms of abusers of the drug and those exhibited by patients suffering from schizophrenia.

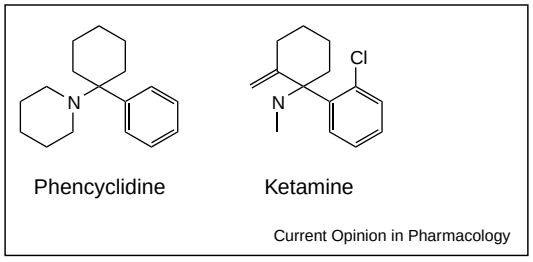
The symptoms of schizophrenia, which usually appear during late adolescence, have been classified as 'positive' (additional to normal experience) or 'negative' (lacking relative to normal experience), occurring alongside deficits in cognitive function. Positive symptoms include hallucinations (generally auditory and visual, but also frequently tactile and olfactory), delusions (often paranoid), thought broadcasting (the belief that one's thoughts can be heard by others), thought insertion (the belief that thoughts of others are being inserted into one's mind) and dysfunction of logical thought patterns. Negative symptoms include depression, anhedonia (inability to feel pleasure), self-neglect and social withdrawal. Dysfunction has been reported across several cognitive domains in schizophrenia, including deficits in working memory, selective attention and mental flexibility (the ability to plan and anticipate outcomes and strategy switching). In particular, deficits in executive function have long been considered to be a core feature of the disease.

PCP and ketamine have been shown to induce a psychosis in humans that closely resembles schizophrenia, and is representative of not only the negative and positive symptoms of the disease but also the cognitive deficits [1]. Chronic PCP abusers have commonly been misdiagnosed as being schizophrenic, whereas PCP administration exacerbates symptoms in chronic stabilized schizophrenic patients [2–4]. Many drugs can cause hallucinations, but the ability of PCP to mirror the symptomatology of schizophrenia almost completely is unparallelled. This extends even to those symptoms considered unique to schizophrenia (e.g. 'thought broadcasting').

Pharmacology of PCP

PCP has a rich pharmacology; its major action is as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) class of glutamate receptor [5]. As PCP is believed to bind to a site within the channel pore that is only accessible when the channel is open, the antagonism is 'use-dependent'. PCP thus acts at the same site as other 'open channel' blockers such as MK801

Figure 1



Chemical structures of phencyclidine and ketamine.

(dizocilpine). These ligands bind in the pore near the ion selectivity filter, which is formed by residues at the 'N/Q/R' site [6,7]. This binding shows stereo-selectivity [8]. The affinity of PCP for this site is approximately 0.2–1.0 μM [8,9], which is consistent with the concentrations of PCP encountered in human plasma in abusers [10]. However, PCP can also inhibit other ion channels, including voltage-dependent sodium and potassium channels, again by binding to a site within the pore of the channel [9,11]. Another ion channel — the nicotinic acetylcholine receptor — is also inhibited by PCP in a non-competitive (but non-use-dependent) manner [12]. In addition, PCP acts on other membrane proteins, producing antagonism of the sigma-receptor, originally viewed as a type of opioid receptor because of its affinity for benzomorphan sigma-agonist opioids [13], and the dopamine and noradrenaline transporters [14,15]. All of these other effects of PCP are less potent than its action on the NMDA receptor, and it is likely that at clinically relevant doses they are not a major component of the molecular action of PCP or its clinical neuropsychiatric profile. Therefore, the main site of action of PCP in the CNS appears to be the NMDA receptor. Nevertheless, schizophrenic patients reportedly show reduced CNS nicotinic receptor activity, elevated limbic dopamine levels, and compromised potassium channel function. Hence actions at these sites might contribute, at least partially, to the unique psychotogenic properties of PCP.

Effects of PCP *in vivo*

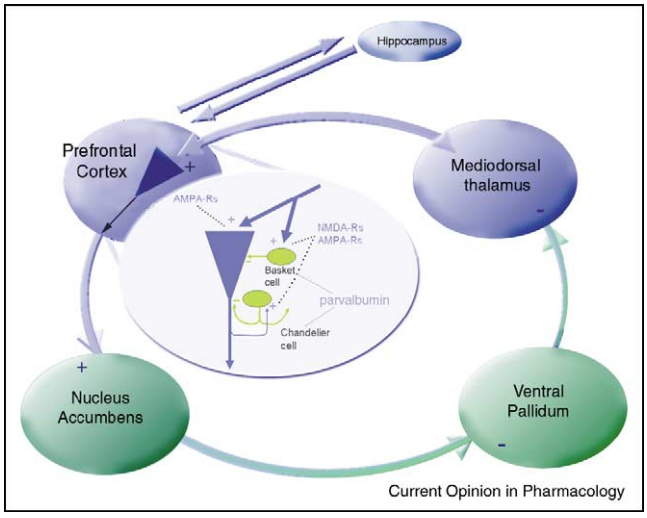
Strong evidence linking PCP exposure to schizophrenic symptoms has led to the glutamate hypofunction hypothesis of schizophrenia, which proposes that schizophrenia is caused by hypoactivity of glutamatergic (and particularly NMDA-receptor-mediated) activity in key pathways in the limbic system. This has been partly supported by evidence of decreased expression of NMDA receptor subunits and associated proteins in the brains of schizophrenic patients relative to controls [16,17].

Naturally, this has led to the use of PCP administration in rodents and primates to model schizophrenia. However, the effects of PCP on the CNS vary dramatically with dose and, until recently, little attempt had been made to find the equivalent treatment regimes in rodents to those producing psychotogenic effects in humans. In rats, acute PCP impairs social interaction [18] and induces cognitive deficits [19], in particular disruption in sensory motor gating, a phenomenon associated with schizophrenia [20]. However, because chronic PCP administration in humans is more likely to lead to a schizophrenia-like psychosis than is a single acute exposure, the effects of chronic PCP treatment in rodents should be more relevant for modelling psychosis. Repeated exposure to PCP reportedly produces a sustained decrease in dopamine turnover within the prefrontal cortex, which is accompanied by a deficit in working memory and prefrontal cortex-dependent tasks in both rats and non-human primates [21,22]. However, relatively high doses of PCP have been used in these studies, and it is well known that high doses of PCP in rodents produce a distinctive pattern of neurodegeneration, affecting primarily the pyramidal neurones of the retrosplenial cortex [23]. This pattern of neurodegeneration is not observed in postmortem tissue from schizophrenic patients, in which interneurones rather than pyramidal neurones appear to be primarily affected, indicating that high doses of PCP are probably not appropriate for modelling schizophrenia.

Neurochemical and pathological correlates of schizophrenia

There is a robust and specific pattern of pathological and neurochemical deficits associated with schizophrenia, involving primarily the prefrontal cortex, thalamus and hippocampus of patients. In particular, prefrontal cortex parvalbumin levels are reduced, indicating dysfunction of γ-aminobutyric acid (GABA)ergic basket cells and chandelier cells. The prefrontal cortex from schizophrenic patients also shows reduced numbers of chandelier cell axon terminals [24–26]. A similar loss of parvalbumin-containing GABAergic interneurones occurs in the hippocampus [27]. In addition, imaging of regional cerebral blood flow and metabolic activity in patients has revealed lower activity in the prefrontal, cingulate and temporal (including the hippocampus) cortical areas, the striatum/accumbens region and the thalamus. The observation of reduced metabolic activity in the prefrontal cortex during performance of a cognitive task has proved a particularly robust finding, and the magnitude of the deficit has been shown to correlate with the presence and severity of negative symptoms and cognitive deficits. Similarly, reduced metabolic activity in the thalamic mediodorsal nucleus also correlates with negative symptomatology [28•]. Conversely, there is evidence that altered metabolic activities within the temporal lobe and related regions of the thalamus correlate with positive symptomology [28•,29–34]. Overall, the evidence strongly suggests that schizophrenia is associated with dysfunction in the corticolimbothalamic circuit, which runs from the prefrontal cortex to the ventral striatum, on to the ventral

Figure 2



The corticolimbothalamic circuit. Accumulating neurochemical, pathological and metabolic evidence suggests that activity in this circuit is dysfunctional in schizophrenia. The inset gives a schematic view of the synaptic connections in the prefrontal cortex between the GABAergic basket and chandelier cells, and the glutamatergic pyramidal neurones. As described in the text, the molecular structure and location of ionotropic glutamate receptors, particularly in the prefrontal cortex, could be critical in triggering the altered activity in this circuit.

pallidum, then to the mediodorsal thalamic nucleus, before returning to the prefrontal cortex (Figure 2). Interestingly, there is increasing evidence that current typical and atypical antipsychotic drugs, such as haloperidol and clozapine, act on this circuit [35].

Modelling schizophrenia

Until recently, no evidence showed that PCP could reproduce these robust metabolic and neurochemical deficits in animals. However, there is evidence that acute administration of low-dose PCP can increase immediate-early gene expression in the prefrontal cortex, indicating increased neuronal activity [36]. This is consistent with evidence that acute administration of ketamine or PCP produces a rapid increase in prefrontal cortex neuronal firing in rodents [37] and prefrontal cortex metabolic activity in healthy human volunteers [38]. However, Tamminga and colleagues [36,39] reported that low-to-moderate doses of PCP in rats caused an initial excitation of cortical areas, followed by a delayed (and presumably compensatory) depression of activity in the prefrontal cortex over a 24 h period. This was detected using both immediate-early gene expression and metabolic activity measurements. Because schizophrenic patients show suppressed prefrontal cortical metabolic activity, this focuses attention on the delayed phase of the response to PCP, rather than the initial phase, as being more relevant to the symptoms of schizophrenia. Interestingly, there is a decrease in parvalbumin expression in the rat prefrontal cortex 24 h after low-dose PCP, suggesting impairment of chandelier cell function [40]. Furthermore, using an attentional set-shift task [41], which assesses prefrontal cortex-dependent cognitive flexibility in rats in the same way as the Wisconsin card sort test used in schizophrenic patients, Egerton *et al.* [42] have shown recently that 24 h after a single low dose of PCP (2.58 mg/kg) there is a specific deficit in the extra-dimensional shift that corresponds precisely to the deficits seen in schizophrenic patients.

Cochran *et al.* [43••] assessed the effect of chronic low-dose PCP in rats (2.58 mg/kg daily for five days) on metabolic activity in approximately 50 brain regions. Whereas the majority of brain regions showed no change in metabolic activity, chronic PCP treatment led to decreased metabolic activity in the prefrontal cortex, as well as within structures of the auditory system. The hippocampus and the reticular nucleus of the thalamus also showed changes in metabolic activity. Once established, these regionally specific changes were maintained if the same dose of PCP was given at reduced frequency (three times per week) for a further 21 days. Intriguingly, this dose regimen also produced a selective reduction in prefrontal cortex parvalbumin expression, strongly indicating impairment of basket cell/chandelier cell function. The ability of chronic NMDA receptor antagonist treatment to selectively suppress the activity of this population of interneurones is supported by the report that ketamine administration to rats for five days reduces parvalbumin expression in hippocampal interneurones [44]. Importantly, in the study by Cochran *et al.* [43••], metabolic changes in the temporal cortex and thalamus, but not in the prefrontal cortex, could be reversed by chronic antipsychotic treatment. This mirrors the clinical observations of the ability of existing anti-psychotic drugs to restore altered metabolic activity in the thalamus and temporal cortex, but not the prefrontal cortex, in patients. This probably reflects efficacy of these drugs against the positive symptoms, but not negative symptoms or cognitive deficits, of schizophrenia.

Interestingly, although this chronic low-dose regime does not cause any overt behavioural effects, it does appear, from preliminary evidence, to induce the types of cognitive deficit seen in schizophrenic patients.

Potential mechanisms

Thus chronic administration of low-dose PCP in rats produces a pattern of neurochemical and metabolic changes that matches almost exactly those observed in schizophrenic patients, with remarkable regional specificity. How might this be achieved? Activity in the corticolimbothalamic circuit is strongly regulated by local GABAergic interneurones, including basket and chandelier cells. Output from the prefrontal cortical pyramidal

neurones is suppressed and coordinated by GABAergic chandelier cells (Figure 2). These chandelier cells are activated by recurrent collaterals from the pyramidal neurones and exert a powerful feedback inhibitory action upon these neurones via synapses onto the axon hillock [45]. The cortical parvalbumin-positive inhibitory interneurones (chandelier cells and basket cells) are unusual in several ways: firstly, NMDA receptors participate in their basal synaptic activation [46,47•]; secondly, they only express low levels of the GluR2 α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor subunit that, when present, renders AMPA receptors impermeable to Ca^{2+} [48,49]; and thirdly, they probably only display NMDA receptor-independent long-term depression of activity, and no long-term potentiation, after high frequency afferent activation [50]. We speculate that administration of PCP acts preferentially to suppress the activation of these interneurones as a result of NMDA receptor participation in their basal levels of activation. Chandelier cells are particularly important for restraining excessive pyramidal neurone activity [45], so this leads to dramatic disinhibition of the pyramidal neurone efferent activity and elevated uncoordinated firing [51,52] throughout the corticolimbothalamic circuit. This corresponds to the transient excitatory phase observed after PCP administration. Suppression of the parvalbumin-containing interneurones would be exacerbated owing to the expression of long-term depression at their afferent synapses and, over the next few hours, compensatory mechanisms (e.g. long-term depression of synaptic efficiency in the thalamocortical synapses [53]) would lead to rebound suppression of activity in the circuit, incorporating maintained suppression of the chandelier cells. This would correspond to the long-lasting metabolic hypoactivity observed in cortical and thalamic regions.

In patients with schizophrenia, damage to the parvalbumin-containing cells can occur through genetic factors, through perinatal trauma (leading to transient episodes of excitotoxicity) or through combination of the two [54,55]. Indeed, these cells are particularly sensitive to AMPA-receptor-mediated excitotoxicity [56] as a result of their relative lack of the AMPA receptor GluR2 subunit allowing direct influx of Ca^{2+} through the AMPA receptors [48]. The deficit might only become apparent many years later owing to the late maturation of the morphological and neurochemical phenotype of the chandelier cells [57]. The fact that the corticolimbothalamic circuit, rather than other parallel corticothalamic network loops, is affected in schizophrenia might reflect the late appearance of parvalbumin expression and chandelier axon cartridges in the prefrontal cortex relative to other cortical areas [58]. The efficacy of D2 dopamine receptor antagonists in treating the positive symptoms of schizophrenia may be related to their ability either to suppress abnormal patterns of pyramidal neurone activity in the prefrontal cortex [59] or to enhance glutamatergic activity in the nucleus accumbens [60], temporal cortex or hippocampus [61].

Conclusions

Thus evidence suggests that PCP can be used in rodents to produce a pattern of metabolic, neurochemical and behavioural changes that reproduces almost exactly those seen in patients with schizophrenia. This has given considerable insight into the processes that lead to the development of the disease, emphasizing the potential importance of NMDA receptor hypofunction in the development of the disease. Evidence is growing that pharmacological enhancement of NMDA receptor function might ameliorate positive and negative symptoms, as well as cognitive deficits, in schizophrenic patients [62]. Furthermore, the finding that chronic PCP treatment in rodents can model schizophrenia closely is of immense importance for the testing of novel antipsychotic drug candidates. Traditional models employed to test for antipsychotic efficacy were based on the dopamine hypothesis and detected ligands with anti-dopaminergic properties. With our understanding of how PCP can be used to reproduce schizophrenia-like changes in the brains of rats, there is now the potential to test for ligands either with efficacy in behavioural tests that mirror the cognitive deficits in patients or with efficacy at restoring metabolic hypofrontality or chandelier cell function. Such assays are not limited to detecting ligands of a single pharmacological class. Thus we are edging closer to a stage where we can predict efficacy in schizophrenic patients (against all classes of symptoms) from the efficacy seen in rodent models. This in turn should greatly facilitate the discovery of improved drug treatments for the disease.

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