

Phencyclidine and Schizophrenia

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Abstract

Schizophrenia is a neurodevelopmental cognitive disorder whose causes are unknown. Much research has been conducted on possible neurochemical origins and effects of the disorder. It is well known that dopamine is involved in the pathology of schizophrenia. However, recently there has also been increasing interest in the role of the N-methyl-D-aspartate (NMDA) receptor in schizophrenia, particularly in its cognitive deficits. In particular, it has been proposed that there is NMDA receptor hypofunction. Importantly, some processes of synaptic formation and elimination, which may be targets of schizophrenia are regulated by the NMDA receptors. Literature on the role of the NMDA receptor in the disorder of schizophrenia has been reviewed.

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Schizophrenia is a brain disorder that affects one percent of the world's population (Klink et al., 2003). According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) schizophrenia can be characterized by cognitive deficits (e.g. deficits in abstraction, executive function, verbal memory, attention) in addition to the positive (e.g. hallucinations, paranoid thoughts) and negative (e.g. flat affect, anhedonia, social withdrawal) symptoms.

While the actual cause of schizophrenia is not known, researchers have hypothesized about the pharmacological causes of the disorder. One hypothesis for the pharmacological basis of schizophrenia is the N-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis (Itokawa et al., 2003). Studies have been done using ketamine and MK-801 (both NMDA antagonists) as models for schizophrenia. However, this paper will discuss the effects of phencyclidine (another NMDA antagonist) treatment on animals in prepulse inhibition and cognitive tasks. Though study in this field is not as extensive as studies on how dopamine regulation is affected by schizophrenia, nevertheless these studies have generated a useful animal model of schizophrenia.

Schizophrenia is a disorder that greatly affects the frontal lobe. Therefore, many of the deficits that schizophrenics show are similar to those seen in patients with frontal lobe damage (Klink, et al., 2003). Previous research on humans has shown that schizophrenics are impaired on cognitive tasks as well as on prepulse inhibition, a sensorimotor gating task (Marcotte et al., 2001). This is due to the intrinsic frontal lobe nature of such tasks, particularly cognitive tasks. Therefore, the use of these tasks in testing animal models of schizophrenia is especially useful.

Animal models of schizophrenia, and other disorders, are useful for research on understanding and treating schizophrenia because with animal models it is possible to mimic and treat different aspects of the disorder separately. This method of research may provide better insight into which systems are compromised in schizophrenia as well as how they would work normally. In addition, using animal models evades the ethical and moral dilemma of using humans as subjects for neurochemical and other studies. Furthermore, although PCP causes some behaviors in animals that are not necessarily seen in people with schizophrenia, such as locomotor activity as well as ataxia, head-bobbing, backward-walking, circling, and head-swaying, many studies have reported the high face, predictive, and construct validity associated with using PCP on animals as a model for schizophrenia (Steinpreis, 1996).

Phencyclidine

Phencyclidine (PCP) is a non-competitive NMDA glutamate receptor antagonist. Past research has shown PCP to be a useful model of schizophrenia psychosis, not only in humans, but in non-human primates and rodents as well. It has been shown that in animals, PCP treatment causes increased apoptosis in the cortex (Wang et al., 2001). This is of particular importance in solidifying the usefulness of PCP as a model for schizophrenia, because the schizophrenic brain repeatedly shows statistically significant levels of cortical apoptosis when compared with controls. Furthermore, PCP has been especially useful in that it can induce positive and negative symptoms as well as cognitive deficits associated with schizophrenia, making it a more valid model for schizophrenia (Javitt & Zukin, 1991). In humans, PCP administration has been known to cause psychotic symptoms so similar to schizophrenia that techniques such as gas

chromatography/mass spectrometry were needed to assist in accurate diagnosis between true schizophrenic psychosis and those induced by PCP use (Steinpreis, 1995). In addition, PCP has also induced psychotic episodes in patients with schizophrenia who are in remission, therefore supporting its usefulness as a model for the disorder.

Furthermore, unlike amphetamine, which has been used extensively in the past to mimic the positive symptoms of schizophrenia, PCP can evoke the negative symptoms associated with the disorder, such as ataxia and impaired social behavior. In the past, few drugs have been able to mimic the negative symptoms characteristic of schizophrenia. In this respect, as well as a model for the cognitive deficits of schizophrenia, PCP is particularly helpful. After administering PCP to animal models of schizophrenia researchers can then try to find treatments for the cognitive deficits and negative symptoms of schizophrenia, which currently are not treated as effectively as the positive symptoms.

Other interesting aspects of PCP are that acute doses have been shown to increase forebrain dopaminergic transmission, while long-term doses seem to reduce frontal dopamine transmission (Jentsch & Roth, 1999). The former finding, increased forebrain dopaminergic function, then is in support of the hyperdopaminergic hypothesis of schizophrenia and explains how PCP can mimic the positive symptoms associated with schizophrenia. The hyperdopaminergic hypothesis of schizophrenia has been used in the past to explain the positive and cognitive deficits of schizophrenia. Therefore, the latter finding, that chronic doses reduce frontal dopaminergic transmission, explains the similarities between PCP induced cognitive deficits and those found in people with schizophrenia. In addition, Sircar & Rudy (1998) also state that at higher doses PCP has

been shown to interact with other neurotransmitter systems, which can again explain its effects on the dopaminergic system.

Cognitive testing

Jentsch et al (1997) conducted an experiment in which 10mg/kg of PCP or 1ml/kg of saline was administered once a day for fourteen days to adult male rats. The rats were previously trained on a delayed alternation task. Two days after the final injection the rats were retested in the delayed alternation task for no more than ten days after receiving their last injection. The experimenters found that the rats treated with PCP had impairments in working memory that were delay dependent. As mentioned previously, the cognitive deficits measured in the delayed alternation task caused by the PCP treatment are very similar to the cognitive deficits experienced by schizophrenics.

Other researchers have also studied the cognitive deficits following PCP treatment. In a study by Wiley et al (2003) the experimenters treated female rat pups with subcutaneous injections of either 10mg/kg of PCP or saline. The pups were injected on postnatal days seven, nine, and eleven. Training on the maze tasks started on postnatal day thirty-four. The task was a delayed spatial alternation task. The results indicated that the rats that received perinatal injections of PCP were impaired in the acquisition of the delayed spatial alternation task, but eventually obtained the level of accuracy that the controls showed. These results are similar to those found by Wang et al (2001) who conducted a similar experiment. However, when Wiley et al (2003) administered dizocilpine, another NMDA blocker, during testing, the PCP treated rats showed a more significant dose dependent decline in percent accuracy. These findings show the cognitive deficits associated with perinatal PCP treatment (slower acquisition in

the delayed spatial alternation task) and how pharmacological challenge with other drugs can heighten these deficits. In addition to dizocilpine, the researchers also administered ketamine, amphetamine, nicotine, and PCP during the testing phase. However, these drugs did not seem to exacerbate the cognitive deficits caused by perinatal PCP treatment.

Prepulse inhibition

Prepulse inhibition is a sensorimotor gating task in which the subject is exposed to a soft pulse (the prepulse) and then to a much louder one. In normal subjects the prepulse acts a cue to reduce the subjects startle reaction upon hearing the louder pulse. Prepulse inhibition is a useful tool for measuring schizophrenia-like deficits in animals. Previous studies have already demonstrated that schizophrenics show deficits in sensory and sensorimotor gating (Martinez, et al., 2000). In addition, prepulse inhibition is a task that can be measured across species. In humans it is related to fundamental cognitive symptoms of schizophrenia and is associated with thought disorder and distractibility. Furthermore, Wang et al (2003) state that repeated perinatal administration of PCP caused cortical apoptosis as well as long-lasting impairments in prepulse inhibition tasks.

In their study, Martinez et al (2000) injected rat pups and juveniles with .5, 1, or 1.5 mg/kg PCP. In addition, they also gave adult rats 5mg/kg of PCP (a neurotoxic dose). The experiments were conducted in a startle chamber where the rats were exposed to the pulse alone, a prepulse, or no stimulus. The results show that the pups and juveniles treated with PCP did not show a reduction in prepulse inhibition. Furthermore, the results also indicate that PCP treated rats had a higher startle magnitude. However, the adult rats treated with a neurotoxic dose of PCP did not show any significant difference

in startle magnitude but did show a significant impairment in prepulse inhibition. In addition, Martinez et al (2000) also administered a neurotoxic dose of PCP to sixteen-day-old pups and tested them on prepulse inhibition. The results showed that the pups, like the adults, showed a significant deficit in prepulse inhibition but did not show a higher startle magnitude. However, the adults showed a greater deficit in prepulse inhibition as compared to the pups. Therefore, these findings suggest that this is perhaps due to developmental changes in brain regions, which might mimic the developmental brain stages of a human. This finding is significant since the onset of schizophrenia tends to be in late adolescence to early adulthood.

Martinez et al (1999) conducted an earlier study similar to that described above. For the experiments on the effects of acute drug treatment on prepulse inhibition female rats were given .25, .75, or 1.5mg/kg of PCP or saline and male rats were given saline or 10mg/kg of PCP. The female rats showed a dose dependent decrease in prepulse inhibition. The males also showed an impairment in prepulse inhibition after repeated injections when tested ten minutes after being injected but not when tested six hours after being injected. In addition, the experimenters also implanted osmotic minipumps or subcutaneous pellets, which delivered PCP continuously to female rats. When the rats were tested three days after implantation there was a significant reduction in prepulse inhibition for both low (2.73mg/day of PCP) and high (5.45mg/day of PCP) levels. Furthermore, when the researchers conducted another test, this time ten days after the minipumps and subcutaneous pellets were removed (following five days of continuous PCP administration), there was no significant difference in prepulse inhibition between the three conditions (saline, low dose PCP, and high dose PCP). These findings suggest

that while NMDA antagonists do cause reductions in prepulse inhibition in rats, NMDA dysfunction does not seem to act alone in sustaining these deficits in people with schizophrenia.

Another experiment, conducted by Wang et al (2001), also studied the effects of PCP on prepulse inhibition. In one study rat pups were pretreated with PCP, PCP plus olanzapine (an atypical antipsychotic drug), or olanzapine on postnatal days seven, nine, and eleven. They were then injected with either saline or PCP (10mg/kg). Their results showed that pretreatment with olanzapine significantly reduced the deficits seen in the PCP group on prepulse inhibition. In another experiment reported in the same article, Wang et al (2001) pretreated pups with either PCP (10mg/kg) or saline on postnatal days seven, nine, and eleven. They then were treated with 2mg/kg of olanzapine or saline twice a day from days twelve to twenty-three before being tested on prepulse inhibition. The results again show that olanzapine reduced the deficits caused by PCP. In still another study reported in this article, the researchers found that olanzapine significantly reduced horizontal locomotor activity caused by PCP (2mg/kg on postnatal day forty-two, thirty-one days after treatment with PCP). This is important because increased hyperactivity is thought to be one manifestation of schizophrenic symptoms (Steinpreis, 1996, Weiner, 2003).

In another study by Wang et al (2003) they again injected rat pups with either saline or 10mg/kg on postnatal days seven, nine, and eleven. However, this time two and twenty-four hours after each injection they also injected the pups again, this time with either saline or 10mg/kg M40403. M40403 was given to see if it would prevent the PCP induced apoptosis and deficits in prepulse inhibition. There was also another group that

was injected with PCP followed by M40403, but for a longer period of time (until postnatal day twenty-four). Some pups were sacrificed on postnatal day twelve for analysis of apoptotic markers while others were used for behavioral testing. Behavioral testing on the prepulse inhibition task began on postnatal day twenty-five. The results showed that M40403 prevented PCP induced apoptosis in the dorsolateral frontal cortex and the olfactory cortex. However, M40403 did not reduce the PCP induced deficit in prepulse inhibition. They also found that in the group that received M40403 treatment up to day twenty-four there was no deficit in prepulse inhibition. Their finding therefore suggests that the deficit in prepulse inhibition may be due to apoptosis caused by PCP.

These results of the studies above further indicate that PCP does cause deficits in prepulse inhibition. The findings also correlate with those noted in Jentsch & Roth (1999) stating that, animals treated with PCP and schizophrenics share a failure to abate their startle response even after exposure to the neutral 'warning' stimulus. Geyer et al (2001) also indicate how effective PCP and other non-competitive NMDA antagonists are at inducing schizophrenia-like deficits in prepulse inhibition, since a much lower dosage is needed to cause the deficit than is needed to cause impairments in locomotor activity.

Conclusion

Cognitive tasks and prepulse inhibition have been shown to be useful tasks in assessing animal models for schizophrenia, not only because patients with schizophrenia show a deficit in such tasks, but also due to their cross species applicability, particularly that of prepulse inhibition. In addition, PCP has been demonstrated as being a very useful drug in inducing schizophrenia like symptoms in humans as well as in animal

models of schizophrenia. Also, PCP has proven to cause these deficits in animals in the standard tasks used in studying people with schizophrenia. Although more studies have been done on the effects of PCP on attention and memory, as related to schizophrenia, these studies have focused more on the effects seen in the hippocampus. In addition, though the NMDA receptor hypofunction hypothesis is a promising pharmacological hypothesis for the chemical basis of schizophrenia, it is relatively new, and as such, there is not an extensive amount of research in this area.

More importantly though, PCP has been shown to be a useful drug in mimicking some of the previously untreated symptoms of schizophrenia, such as the cognitive deficits as well as the negative symptoms, which other drugs have not been able to do. In addition, PCP's effects on the dopamine system make it an even stronger model for schizophrenia, as there is strong evidence for abnormal dopamine regulation in schizophrenia. More research has been on the hyperdopaminergic hypothesis of schizophrenia than on the NMDA receptor hypofunction hypothesis. Therefore, given the properties of PCP and the deficits it causes, it would be useful in understanding and treating cognitive deficits of schizophrenia to study this area more. However, PCP, by itself, can not be a very effective model for schizophrenia. As was stated earlier in this paper, PCP interacts with other neurotransmitter systems, such as the dopaminergic system, in a dosage dependent manner. Furthermore, PCP does not equally effectively mimic ever aspect of a disorder as complex as schizophrenia. Rather, for a disorder with such widespread effects on the brain as schizophrenia has, many separate models, each mimicking a different symptom of the disorder, may be necessary.

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