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Psychosis: Atypical Limbic Epilepsy versus Limbic Hyperexcitability with Onset at Puberty?

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Abstract

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Phencyclidine (PCP), Ketamine (Special K) and MK-801 are non-competitive NMDA antagonists that produce acute psychosis in humans. The psychosis produced by these psychomimetic drugs is indistinguishable from schizophrenia and includes both positive and negative symptoms. This drug-induced psychosis occurs after puberty in humans. This brief review argues that this psychosis is an atypical form of limbic epilepsy based upon MK-801 induced spike-and-wave activity in rats and based upon increased blood flow and metabolism in brain of patients with psychosis caused by these psychomimetics. Moreover, there is a specific limbic thalamcortical psychosis circuit that mediates cell injury in limbic cortex of rodents and may mediate this PCP-induced psychosis in humans. It is proposed that this thalamocortical psychosis circuit develops at puberty and can mediate psychosis at puberty and in adulthood by PCP and ketamine-induced psychosis, and possibly in schizophrenia, bipolar disease and other psychotic states. Finally, based upon this developmentally regulated psychosis-epilepsy related thalamocortical circuitry, it is proposed that anti-epileptic drugs that promote GABAergic mechanisms might decrease the probability of episodic psychosis from any cause.

Keywords: psychosis, epilepsy, ketamine, PCP, phencyclidine, NMDA antagonists, anti-convulsants

1. Introduction: PCP and Ketamine Produce Psychosis in Humans After Puberty

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PCP (Phencyclidine), also called angel dust, Peace Pill, crystal, horse and horse tranquilizer, is an abused and addictive drug that has hallucinogenic properties [1]. PCP was the drug that Rodney King putatively took when he became bezerk and was subdued/attacked by the Los Angeles police, an event that precipitated the Watts riots. Ketamine, also called Special K by the addicts that abuse it, also has hallucinogenic properties.

Both PCP and Ketamine produce an acute psychosis in adults, and the psychosis produced by PCP is indistinguishable from acute schizophrenia in that negative symptoms also accompany the psychosis [2][3][4][5][6][7][8]. The occasional individual who takes PCP becomes extremely violent and can become "super human" and accounts for the frequent use of padded rooms in the 1960s and 1970s when PCP was frequently abused – the rooms being used to confine these individuals without hurting themselves or others.

Both PCP and Ketamine are non-competitive NMDA glutamate receptor antagonists. These drugs are structurally similar to the more potent MK-801, which has been used for decades to block NMDA receptors in experimental studies. PCP and Ketamine share the property that they do not produce psychosis in children. Indeed, Ketamine is still used as an anesthetic in children since it is very safe in that it does not cause a drop in blood pressure, does not affect respiration/breathing and is not associated with the hallucinations and psychosis that occurs in adults given this drug. Ketamine given to adults as an anesthetic causes a dissociative state where patients do not respond to the surgery or other intervention, remain passive, may have hallucinations, but experience some feature of the pain of surgery. The fact that ketamine does not produce analgesia has led to the uncommon use of the drug as an anesthetic for adults [9] except for the management of post-operative pain and in intensive care units where it can be useful for placing lines and other devices without causing respiratory suppression or falls in blood pressure.

PCP, Ketamine and MK-801 are called non-competitive NMDA receptor antagonists because they do not bind at the same location on the receptor where glutamate binds. Instead, PCP and ketamine bind within the calcium channel of the NMDA receptor and block ion flow through the channel. Though non-competitive NMDA antagonists are potent hallucinogens in humans, even the competitive NMDA antagonists can produce psychosis in humans at high doses. This short review examines the effects of these drugs in humans and animals and proposes a circuit that may mediate the injury to limbic cortex that these drugs produce in rodent animal models, and the circuit that likely mediates psychosis from these drugs in humans. The nature of the circuit also suggests it might mediate psychosis in many disorders including schizophrenia and bipolar disease, and that anticonvulsant drugs with GABAergic properties might be useful in decreasing the probability of psychosis from any cause.

2. PCP and Ketamine INCREASE Blood Flow and Metabolism in Limbic Structures in Humans

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A number of studies have examined blood flow and glucose metabolism in the brain of individuals who have been given ketamine. These studies have included normal volunteers, as well as controversial studies in schizophrenics. All of the studies have shown similar findings. That is, there is INCREASED blood flow and metabolism in various structures in the brain of animals and man including limbic cortex, thalamus and other brain regions [3]10][11][12][13][14]. Though these studies have been interpreted in various ways, the intriguing feature to all of them is that blocking an excitatory NMDA glutamate receptor led to INCREASED blood flow and metabolism in the brain. The explanation for why this occurs is still debated, and may be accounted for by findings described in animals below. That is, the majority of NMDA receptors may be found on GABA neurons. Blocking the NMDA receptors on the GABA neurons would decrease GABA release, and result in activation of brain circuits, and thus result in the INCREASED blood flow and metabolism seen in humans after administration of these drugs.

To the current authors knowledge, it is not clear whether detailed EEG studies have been performed in patients who have taken PCP or ketamine and who are psychotic. This might be difficult given the psychosis. In the epilepsy literature, however, there are many reports of psychosis associated with a seizure itself, in the

post-ictal state, and during periods between seizures [15][16][17][18][19][20]. The relationship of these psychotic states that occur during and just after documented epileptic seizures and the psychoses associated with PCP, ketamine, schizophrenia, mania in the bipolar patient and other psychotic disorders is not clear.

The general hypothesis of this review is that all psychoses are associated with an excitable brain, in specific psychosis circuits that are over-activated. Even if the psychotic state is not associated with traditional electrical changes associated with classical types of epilepsy, the data would suggest that PCP and ketamine activated psychosis are associated with increased blood flow and metabolism in brain, and hence are likely to be associated with increases of electrical activity. This drug induced, increased electrical activity would be quite abnormal, and would appear to be continuously present while the drug was present in high enough concentration.

There is also data to suggest that non-drug induced psychoses – or at least hallucinations – are also associated with increased flow and metabolism in focal areas of brain including the limbic system [21]. This again would suggest abnormal electrical activity. As noted below, we postulate that traditional anticonvulsant drugs might prevent this abnormal electrical activity.

3. PCP, Ketamine and MK-801 Produce Hyperexcitability versus Epileptiform Activity in Rats

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Large doses of ketamine produce anesthesia in rodents, horses and man. This anesthesia in man, however, has the unusual feature of producing a dissociative state where the patient is still aware of surroundings and certainly able to feel and experience pain, but is unable to move or respond. The explanation for this unusual and almost unprecedented “dissociative” state has been elusive. The closest is a hypnotic state.

The accepted mode of action of ketamine, PCP and MK-801 is that these drugs produce psychosis as a result of increased “hyperexcitability” in limbic circuits [14][30][32][34]. Olney et al proposed that NMDA-antagonists produce this hyperexcitability by blocking NMDA receptors on GABAergic neurons, resulting in decreased firing of GABAergic inhibitory neurons, resulting in increased excitability in limbic circuits [30] [32]. This concept was supported by data from our group suggesting that MK-801, PCP and ketamine specifically blocked NMDA receptors on GABAergic neurons in the reticular nucleus of thalamus that led to decreased GABAergic inhibition of thalamic projection neurons, and hyperexcitability in limbic thalamo-cortical circuits [33][34].

An alternative explanation, that is simply an extension of the same mechanism, is that the NMDA antagonist drugs produce a type of seizure that is associated with psychic and motor paralysis. Though difficult to prove in humans, studies in rats have shown that administration of MK-801 produces spike and wave discharges in central brain structures that are akin to epileptiform activity seen in some types of human epilepsy [10][22].

This data that MK-801 might produce epileptiform activity in limbic circuits is certainly contrary to the large majority of the epilepsy literature. Non-competitive and competitive NMDA antagonists have been used to suppress various types of epilepsy in many types of models including status epilepticus [23][24]. However, there are still no clinically used drugs with this mechanism of action. In addition, we propose that non-competitive NMDA antagonists will increase excitability and even produce epileptiform activity in some limbic circuits [22] [25]. This deserves more study, with electrodes specifically targeted at posterior cingulated limbic cortex and limbic thalamus/anterior thalamic nuclei.

4. PCP, Ketamine and MK-801 Injure and Kill Neurons in Cingulate Cortex of Rats After Puberty

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Not only do these drugs causes epileptiform activity in rodents, they also damage and kill neurons in limbic cortex. Olney and colleagues were the first to demonstrate that PCP, ketamine and MK-801 produced vacuoles in the cytoplasm of pyramidal neurons in posterior cingulate and retrosplenial cortex of adult rats [26]. Our group showed that this neuronal injury was associated with the induction of Hsp70 and other heat shock proteins in these neurons, showing that the injury was associated with denatured intracellular proteins [27]. Various groups demonstrated that high doses of these drugs killed neurons in the same brain regions. We showed that high doses of PCP induced Hsp70 in various neurons throughout the limbic system including cortex and thalamus [28].

Because ketamine administered prior to puberty in humans did not produce psychosis, we tested whether administration of these drugs prior to puberty would produce brain injury or not. Indeed, PCP or ketamine administered prior to puberty in rats did not injure cingulate cortex [29]. This age-related injury has been observed independently by many groups in both male and female rodents [30][31].

5. GABA Agonists Prevent the Injury Produced by PCP and Ketamine in Rats

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After the discovery by Olney and colleagues that PCP and ketamine produced vacuoles in neurons in cingulate cortex, they then showed that systemic injections of valium or Phenobarbital prevented the injury [32]. They suggested that the protection was due to GABAergic agonist properties of both drugs, and that the protection was due to activation of GABA receptors on injured neurons; and that NMDA antagonists produced injury by blocking NMDA receptors located on GABAergic neurons. This interesting model has with stood the test time, and has been refined by studies described below. As described in the next section, we have gone on to show that injection of GABA agonists into anterior thalamus prevents the injury to limbic cortex produced by systemic PCP or systemic ketamine [33]. Thus GABA agonists prevent limbic cortex injury by acting on GABA receptors in thalamus.

6. Identification of Thalamus as one Site at Which NMDA Antagonists Act: Limbic Thalamocortical Circuits that Mediate Limbic Cortical Injury in Rats Produced by PCP, Ketamine and MK-801

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With the discovery of PCP/ketamine/MK-801 induced neuronal injury, it was immediately assumed that this probably occurred because of blockade of the various receptors in limbic cortex. However, our group and other groups found that injections of PCP, ketamine or MK-801 directly into limbic cortex did not reproduce the injury observed following systemic injections of these drugs. In addition, injections into other regions also did not appear to reproduce the injury. This conundrum was solved, at least in part, by our group. We showed that bilateral injections of MK-801 into anterior thalamus, but not bilateral injections into cingulate cortex, produced the injury in cingulate/limbic cortex [33][34]. Even more importantly, we showed that bilateral injections of a GABA agonist (muscimol) into anterior thalamus completely blocked the injury in cingulate cortex produced by systemic injections of MK-801 [33][34]. Thus this data conclusively showed that PCP, ketamine and MK-801 act on NMDA receptors in anterior thalamus to produce the injury in cingulate cortex – the cortical target of the anterior thalamic nuclei. In addition, drugs acting at GABA receptors in ANTERIOR THALAMUS reticular nuclei prevented the injury produced in limbic cingulate cortex.

Based upon these results, we developed an anatomical model that explains the findings that have been obtained in the rat studies to date (Figure 1). The essential part of the model is that a nucleus in thalamus, called the reticular nucleus, is the major inhibitory output to the relay nuclei in anterior thalamus. We proposed that PCP, ketamine and MK-801 block NMDA receptors on the GABAergic neurons in reticular

nucleus of thalamus (Figure 1). This resulted in decreased GABA release that led to markedly increased firing of anterior thalamic neurons that then excited and led to increased firing of cingulate cortex neurons and eventually injury in the limbic cortical neurons (Figure 1). Administration of GABA agonists to anterior thalamus inhibited anterior thalamic neurons and prevented the injury produced by systemic PCP and ketamine [33][34].

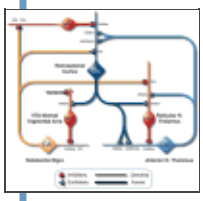

Figure 1

Circuits that are proposed to mediate injury to glutamatergic (GLU) pyramidal neurons in Retrosplenial Cortex of adult rodents produced by phencyclidine (PCP), ketamine or MK-801. GABA neurons are pictured in Retrosplenial Cortex, Reticular Nucleus of ...

Since this circuit mediates the injury produced by PCP and ketamine and MK-801 in adult rats, we proposed that the same circuit might mediate the psychosis produced by these drugs in humans [34]. We proposed that this is the PCP/angel dust/horse "psychosis circuit". It is possible that this same or a very similar circuit might mediate the psychosis observed in other conditions including schizophrenia and bipolar disorder [34][35][36].

7. Typical and Atypical Antipsychotics Prevent the Injury Produced by PCP, Ketamine and MK-801 in Rodent Cingulate Cortex

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Some of the best evidence that the circuits outlined in Figure 1 that mediate injury to limbic cortex are related to psychosis comes from studies of antipsychotic medications. Our group was the first to show that haloperidol, the typical antipsychotic drug often used to treat acute psychosis also decreases the injury in limbic cingulate cortex produced by PCP, ketamine and MK-801 [37]. In addition, administration of atypical antipsychotic medications also used to decrease acute psychosis also decreases the injury in limbic cortex produced by PCP, ketamine and MK-801 [28] [38] [39][40]. Of interest, the potency of the atypical antipsychotic medications to decrease psychosis in humans is similar to the potency of these drugs to decrease limbic cortical injury in rats due to MK-801 [35]. Hence, the parallel between anti-psychotic efficacy and neuroprotective efficacy appears to be very good. Against this argument, however, is the observation that other compounds that are not known to be antipsychotics also protect against the cortical injury produced by PCP, ketamine and MK-801 in rats [41].

8. Implications of Psychosis as a Type of Limbic Epilepsy in Humans that Begins at Puberty

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The above data show that non-competitive NMDA antagonists injure cingulate/limbic cortex in rats and that this injury is prevented by typical and atypical antipsychotic medications. In addition, the NMDA antagonists produce the injury by acting on NMDA receptors in anterior thalamus, and GABA agonists prevent the injury by acting on GABA receptors in anterior thalamus and likely other regions [34][41]. In humans, NMDA antagonists including PCP and ketamine are potent hallucinogens and psychomimetics, with the effects of PCP mimicking the psychosis observed in humans. We propose that the circuits that mediate cortical injury in rodents mediate the psychosis in humans. In addition, we propose that the psychosis produced by these drugs is a type of limbic epilepsy since rodents given these drugs have epileptiform activity [22]. It is possible that the PCP induced psychosis in humans is also a type of limbic epilepsy, and that other forms of psychosis in humans also represent an atypical form of limbic epilepsy. This needs to be investigated further.

The importance of the above line of reasoning is that psychosis of all forms might be treated and viewed as a type of epilepsy; that is, they might be treated with anticonvulsants. This is not a foreign idea since bipolar disease has been treated with valproic acid for some time and more recently with the anticonvulsants including lamotrigine [42][43]. The implications of the above arguments are that all types of psychosis might be decreased in frequency with chronic treatment with anticonvulsants. It is possible that agents with GABAergic mechanisms of action might be the most useful, though detailed studies will be required. It is also possible, that individuals at high risk for psychosis – including a family history of bipolar disease or schizophrenia and possibly with appropriate biological markers – might be considered for prophylactic therapy with anticonvulsants with excellent safety and side effect profiles. Such therapy might be started just before puberty when the proclivity for psychosis – both from PCP and from schizophrenia – appears to have its onset.

Footnotes

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References

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