Phencyclidine/Schizophrenia: One View Toward the Past, The Other to the Future

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The history of the chemical synthesis and animal/human pharmacology of phencyclidine is documented. From its early use as a general anesthetic, chemical model of schizophrenia, and drug of abuse, phencyclidine has had a checkered history. Research with this agent and its chemical derivatives like ketamine has had a solid foundation for just a beginning to understanding the neuropathology of schizophrenia.

Key words: phencyclidine/drug model/drug of abuse

Synthesis and Animal Testing of Phencyclidine

The history of phencyclidine begins with 2 Parke Davis Company medicinal chemists. Dr Harold Maddox discovered a new chemical organic Grignard reaction. It led to the synthesis of phencyclidine (which was later given the clinical investigation number, CI-395) on March 26, 1956.1 Pharmacologist Dr Graham Chen and his associates received the compound from Maddox on September 11, 1957. They showed that it caused an excited drunken state in rodents, but a cataleptoid immobilized state in pigeons. Their studies were extended to a large number of animals.2 The researchers were amazed with its unusual pharmacology. Hence, Dr Maurice Seegers, Head of Pharmacology at the University of Michigan, was contacted as their pharmacology consultant. At the time, one of the authors (E.F.D.) was a young assistant professor of pharmacology in his Department. Dr Seegers suggested E.F.D. study phencyclidine further. He arranged to obtain a Parke Davis grant to do so. The compound produced canine delirium. In monkeys, it was a remarkable anesthetic agent. Years later, the findings were published in order to stimulate basic scientists to study the mechanism of action of this unusual drug.3

First Human Study of Phencyclidine as a General Anesthetic

In 1957–1958, after sufficient animal toxicity testing, phencyclidine was given to humans undergoing surgery. Dr J. E. Gajewski from Parke Davis was the person responsible for its clinical development. He contacted Dr F.E. Greifenstein, Chair of Anesthesiology at Wayne State University. The first phencyclidine human study was initiated at Detroit Receiving Hospital. As in monkeys, phencyclidine was a safe anesthetic in humans. However, some patients had severe and prolonged postsurgery emergence delirium. They stated that did not feel their limbs, as if they were sensory deprived.4 Dr Greifenstein contacted Dr John S. Meyers, Head of Neurology at Wayne State University, to do further studies. They concluded that phencyclidine produced a “centrally mediated” sensory deprivation syndrome.5

Critical Psychiatric Role of the Lafayette Clinic, Michigan Department of Health, Detroit

When Dr Jacques Gottlieb came to the Lafayette Clinic in 1955 as its Director, he made research in schizophrenia its primary focus. He brought together a group of psychiatrists, psychologists, and basic science investigators to explore his theory that schizophrenia was a brain disorder. We approached research in schizophrenia in a multitude of ways, examining the hypothesis that the disorder was caused by a defect in carbohydrate metabolism. We attempted to induce model psychoses through psychotomimetic drugs, sensory isolation, and sleep deprivation. Phencyclohexyl piperidine (phencyclidine, Sernyl, PCP) came into our hands at the Lafayette Clinic after Meyer et al.5 reported a number of postoperative psychoses associated with its use.

During the 1950s, there was enormous interest in sensory isolation, and the description of the drug’s effect suggested that “interoceptive” sensory isolation might result from the administration of phencyclidine at dosage levels which permitted the subject to remain awake and communicative. Essentially, the drug caused the central nervous system to be isolated from peripheral sensory influx. Working with Bert Cohen and Gerald Rosenbaum—and later, Ed Domino—we then decided to design an experiment in which we would give the drug to a large group of psychiatric residents and medical students in order to document its behavioral, neurological, and physiologic effects. When administered intravenously to control
subjects at a dose level of 0.1 mg/kg, the drug produced a predictable series of changes, mimicking the primary symptoms of schizophrenia. Initially, alteration of body image occurred, with a loss of body boundaries and a profound sense of derealization. Then, feelings of estrangement and loneliness ensued, sometimes associated with an intensification of dependency needs and an attachment to the observer. Progressive disorganization of thought, inability to maintain a set or to concentrate, negativism and hostility all followed. Some subjects became catatonic, and many had dream-like reveries in which they felt as though they were in a different setting at a different time. Genuine hallucinations were not characteristic effects of the drug. Distortions of body image and depersonalization were a universal reaction to phencyclidine and occurred just prior to the other deficits in thinking and affect. Our group hypothesized that the reduction of proprioceptive feedback or impairment of central integration and interpretation of input from this sensory modality somehow mediated the effect of the drug.

We implemented a number of psychological tests, like reaction time and other measures of attention, to assess this hypothesis. We compared the effects of phencyclidine with these tasks to data produced by a control group given LSD-25, or amobarbital. In addition, we administered the same tests to a group of chronic schizophrenic subjects in an attempt to determine how closely the performance of control subjects under each of the drugs approximated that of schizophrenic patients. The results clearly demonstrated that phencyclidine produced severe impairments beyond those attributable to sedation, by comparison with amobarbital or to some general psychotomimetic factor as indicated by comparison with LSD-25. Also, phencyclidine was the only drug to produce the level and pattern of deficits shown by the criterion group of schizophrenic subjects. We drew the inference that phencyclidine resulted in schizophrenic-like primary attention and cognition deficits, while LSD-25 simulated secondary phenomena, as hallucinations. These findings were consistent with the hypothesis that there was some disturbance in proprioceptive feedback mechanisms, which accounted for both positive and negative symptoms in the phencyclidine state and in chronic schizophrenia.

With the hypothesis that phencyclidine acted through a disruption in body feedback systems and that such a disturbance already exists in schizophrenia, we designed a methodology to observe the effects of phencyclidine in chronic schizophrenic subjects. The results were quite vivid. Phencyclidine produced profoundly disorganized regressive symptoms in these patients. Their thought disorders greatly intensified, and they manifested considerable affective expression. It was as though the acute agitated phase of the illness had been reinstated. Chronic patients generally became more assertive, hostile, and unmanageable. Unexpectedly, some of the behavioral changes persisted from 4 to 6 weeks after phencyclidine injection in these patients. In these chronic schizophrenic patients, sexual acting out with professions of love toward personnel was observed. One patient screamed, “I want to f—k, I love to eat, I love to f—k. Can I help it?” Another patient wanted to be kissed and fondled but the warmth and amiability were transient. The drug was given to an acute catatonic patient who was completely unresponsive to it. Two days later, he emerged from his catatonia and remembered that he felt as though he were returning to earth from another planet. The responses may have been more dissociative in nature but the increase in affectivity was remarkable in patients who had been withdrawn and uncommunicative for years.

Rodin et al. studied the electroencephalographic responses to different doses of phencyclidine. The drug produced “rather profound slowing of the electroencephalogram (EEG) with pronounced theta activity.” The slowest frequencies were between 3 and 4 cycles/sec. It was interesting that the psychotomimetic effects of phencyclidine were observed in the absence of definitive EEG changes. When the EEG changes occurred, the psychotomimetic effects preceded them by at least 1 to 2 minutes. The EEG effects disappeared in a period of 15 to 30 minutes. Changes can be contrasted with the EEG changes induced by LSD-25. This agent produced a progressive EEG desynchronization. The records became lower in voltage and alpha rhythm decreased. The increase in fast activity was not actual but a result of a decrease in the slower frequencies, which allowed fast activity to become more prominent.

Since the administration of phencyclidine accentuated schizophrenic symptoms, we concluded that the drug affected some fundamental aspect of the disorder. At that time, we believed this feature involved central integration of body input or a disturbance in the proprioceptive feedback system. The pharmacology of the drug was not at all understood, particularly its effect upon neurotransmitters such as glutamate and its receptors.

Having observed that chronic schizophrenic patients tolerated sensory isolation with somewhat less tension and discomfort than control subjects, and in view of the possible intimate relationship between the phencyclidine state and schizophrenia, we designed a controlled experiment to observe the reactions of control subjects injected with phencyclidine under sensory isolation conditions. We collected data including both the immediate observations of the subjects and their retrospective accounts of the experience. We found that the manifest psychotomimetic phenomena usually produced by phencyclidine under nonisolation conditions were markedly attenuated under isolation. The subjects were awake and able to report on their experiences, at least retrospectively, as “nothingness” and total emptiness, with many analogizing this state with death. By contrast to nonisolation experiences with the drug, the subjects felt calm and self-controlled. It was evident that the usual psychotomimetic effects of

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Phencyclidine required exteroceptive inputs for their arousal. The phencyclidine-engendered state resembled schizophrenia to the extent that subjects under the drug tolerated sensory isolation in the manner characteristic of the schizophrenic patients. Perhaps, both the model psychoses of phencyclidine and the clinical psychoses of schizophrenia produced a disturbance in the capacity of the organism to filter and interpret a normal sensory input load. This deficit resulted in generalized aversion to the complex and dynamic influx that is characteristically provided by the normal sensory environment. This finding may explain withdrawal in chronic schizophrenia as a self-imposed form of sensory isolation to compensate for a geared-down and distorting reception interpretation system.

When our human laboratory research with phencyclidine ended in 1962, it was difficult to assess its value. Certainly, the behavioral information this work provided was useful to those clinicians who began to see the “street psychoses” in the late 60s. The fascinating human picture also stimulated considerable animal research, and that work began to provide important data on the physiology of these psychotic states. Of importance to us was the finding that sensory isolation attenuated phencyclidine psychoses. That observation altered our approach to schizophrenia in the early 60s, when acute and chronic patients were no longer subjected to the bombardment of “total pushing” whether in milieux, individual psychotherapy or family therapy. We had come to respect withdrawal as the patient’s only way of modulating intolerable sensory input. The work of Venables and Wing which correlated physiologic arousal in schizophrenic patients with social withdrawal can be analogized to this model psychosis research. Spohn described a comparable phenomenon when he found that schizophrenic patients in an experimental psychotherapeutic program deteriorated when compared with patients who were treated less intrusively. Through the years, as a psychiatrist E.D.L. has often seen schizophrenic patients intensively treated by a messianic therapist who caused them to profoundly regress under this onslaught, only to recover in the benign isolation of a state hospital.

It was astounding to us that phencyclidine became a major street drug of abuse. It was called PCP. Few of our volunteer subjects were ever willing to take the drug a second time. One former resident still recalls her PCP experience as intensely psychologically painful.

In the 1960s and 1970s, other than for alcohol, PCP became the most common cause of emergency room admissions related to drug-induced psychoses in the Detroit metropolitan area. One chronic PCP user whose waxing and waning psychosis was expressed in awesome outbursts of rage virtually destroyed our seclusion room at Harper Hospital. Across the street at Children’s Hospital, Dr Regina Aranow saw 2 or 3 PCP poisonings per month.

At the time of this research, there was a debate over the usefulness of drug-induced model psychoses. Some stated that hallucinogenic drugs could not possibly tell us anything about schizophrenia and that their biochemistry would have no relationship to a putative biochemistry of schizophrenia. It was certainly true that no drug given in an acute laboratory experiment, or if taken illicitly, could simulate a naturally occurring psychosis requiring years for its development; yet, there were aspects of the PCP subjective experience, and the behavioral and cognitive changes it induced, that were remarkably consistent with the psychopathology of some forms of schizophrenia. It was thus hard to accept the conclusions of some that the PCP research could tell us only about PCP and absolutely nothing about functional psychoses.

Although we ended our clinical research on phencyclidine as a drug model of schizophrenia in the early 1960s, others began to look at this drug and its related dissociative anesthetic, ketamine, in much the same way. Payne in 1972 reported that phencyclidine was the only drug capable of producing the specific behavioral abnormalities of chronic schizophrenia in normal people. In 1979, a workshop was held at the annual meeting of the American College of Neuropsychopharmacology to stimulate further interest and research. That workshop resulted in a book summarizing research to that date. At that time, we summarized the symptoms and comparisons of chronic schizophrenia and those induced by phencyclidine and other models of psychoses as listed in table 1.

Since 1981, a remarkable number of advances in our knowledge of phencyclidine, ketamine, and schizophrenia were made. But in the late 1980s, this research area needed a strong push forward. That happened when Javitt and Zukin in their review reported that N-methyl-D-aspartate (NMDA) hypofunction as induced by PCP was a model for schizophrenia. NMDA receptors might be damaged by any number of factors, including excitotoxins or ischemic insults, both perinatally and during adulthood. At the time, they noted that many of the abnormalities of chronic schizophrenia were not ameliorated by neuroleptics, suggesting that they are poorly accounted for by the dopamine model of schizophrenia.

In 1994, Krystal et al reported on mental effects of low doses of ketamine. They found the same cognitive and affective changes that occur with PCP when ketamine was infused into normal volunteers. Thought processes became concrete and over personalized. Loose associations, tangentiality, perseveration, and thought blocking were also common. The thought disorder was indistinguishable from the thought disorders in a group of schizophrenic patients. Because ketamine did not induce auditory or visual hallucinations, the symptom picture was not precisely comparable to that which occurs in schizophrenia. However, the investigators concluded “Despite the failure to generate hallucinations, ketamine produces symptoms in healthy subjects that resemble the negative symptoms in...
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The Krystal group confirmed our observations of some 25 years earlier that LSD-25 induces a clinical syndrome resembling acute schizophrenia, while the NMDA antagonist induced the more chronic state.

Useful but a Limited Model

Although the overlap of symptoms of schizophrenia and phencyclidine/ketamine is impressive, they vary in intensity and presence. Many investigators such as Olney and Farber, Tamminga et al, Abi-Saab et al, Adler et al, Jentsch and Roth, Lahti et al, Goff and Coyle, Sharp et al, Avila et al, Tsai and Coyle, Straub and Weinberger, and Stahl concluded that NMDA receptors are hypofunctional after phencyclidine/ketamine as well as in schizophrenia. However, a very large literature indicates a major disturbance of gamma aminobutyric acid (GABA) interneurons as the primary and not secondary neuropathology of schizophrenic patients. NMDA antagonists block NMDA actions of glutamate on GABA interneurons. Postmortem neuropathologic findings involve GABA interneuron circuitry.

It is quite clear that schizophrenic brains show significant neuropathologic changes, only some of which are produced by phencyclidine. Chronic schizophrenic patients have dilated cerebral ventricles. In some aspects, phencyclidine is producing central effects quite different from what is actually happening in the pathology of chronic schizophrenia. The putative cytoarchitectural changes that occur in schizophrenic cortex over the years have been described in detail. There is a thinner cerebral cortex in lamina 2 and 3, reduced neuron size, smaller and more dense neurons, decreased axon dendrite arborization, reduced neuropil volume, and decreased dendritic spines. Mentally normal persons who die have marked grey matter dendritic spine density, in contrast to what occurs in schizophrenic brain. Many of the neural elements that exist in normal neocortex are also present in schizophrenia. However, this is not marked as in normal brain. Apparently, schizophrenic brain neurons have a deficiency of unknown neurotropic factors. A view of the future will surely some day include a very detailed neuronal/glial map of normal vs schizophrenic brain. We have just begun to travel that new path in the past decade or so. The creation of that brain map will need inputs from many different basic and clinical neuroscience specialists. However, the map may be created more rapidly than one might imagine with the research tools available today. Understanding phencyclidine/ketamine actions represents one small step along the future path of clarifying the complex neurobiology of schizophrenia. Their great value may have been stimulating additional research as opposed to providing a definitive model.

Funding

Supported in part by the Psychopharmacology Research Fund 361024.

Acknowledgments

The authors wish to acknowledge Dr Jacques Gottlieb and the former Lafayette Clinic of the Michigan Department of Health that made the clinical research described possible. The authors have declared that there are no conflicts of interest in relation to the subject of this study.
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