The dawn of a new age: pcp essay

April, 1956 : The pharmaceutical company Parke & Davis first synthesize what they believe to be the perfect anesthetic (Souza, 1995). When administered to patients, it causes a completely dissociative state, with no significant respiratory or cardiovascular depression. Patients appear to be awake, eyes open, breathing normally. but are unaware of their surroundings or the procedures being performed upon them (Souza, 1995).

Indeed, this is the perfect drug. Unfortunately, like all good things, this one has a darker side. 15% of patients awake from their slumber with what appeared to be an acute case of paranoid schizophrenia (Peterson; Stillman, 1978). The drug is PCP, and to this day it is the scourge of the underground drug community, and the focal point of intense scientific research.

Parke Davis and Company did not know how terrible, and wonderful, a discovery they made that day; but our world has been changed forever because of it. quite possibly for the better.

The Dust of Angels Phencyclidine, more commonly known as PCP, is a polycyclic compound belonging to the arylcyclohexylamine class of chemicals [figure 1. 0] (Souza 1993). In pure form, it is a white powder which readily dissolves in water. The cyclohexamines are known for their the potent neurological effects, with PCP being the most potent. Almost every variation has been administered to, or abused by, humans at some time (Nintey Fifth Congress, 1978). All these compounds have similar pharmacological effects, which vary considerably according to the amount administered.

Small doses produce a ‘ drunken’ state, in which subjects report a numbness in the extremities, while some species (like dogs and cats) become quite excited (Halberstadt, 1995).

Intermediate doses have anesthetic and analgesic effects, with the psychic state resembling sensory isolation with one important exception: the sensory impulses (when tested electrophysiologically) reach the neocortex but “ the neuronal signals are grossly distorted” (Halberstadt, 1995). Large doses, especially of PCP, may produce convulsions. Any dose produces cataleptoid muscle effects (Halberstadt, 1995). All the chemicals in this class produce a range a physiological effects, including tachydardia and hypertension (Halberstadt, 1995).

Unlike the other cyclohexamines, however, PCP causes severe “ emergence delirium” when taken in moderate to anesthetic quantities (Halberstadt, 1995). On the other hand, ketamine, a close cousin of PCP, produces depressant effects which are more amplified than PCP without the psychotic aftereffects (although hallucinations are reported by patients during sedation, (Halberstadt, 1995)).

In special cases, ketamine is still used as an anesthetic. (C. H.

Badenhorst M. D, personal communication). Ten years after its initial discovery, phencyclidine found a new audience in the scientific and underground drug culture communities (Nintey Fifth Congress, 1978). At this time, a few Freudian psychologists carried out unauthorized experiments in which perfectly healthy patients were given PCP and observed (Nintey Fifth Congress, 1978).

Although their research did not provide much useful data, it did begin a revolution in our knowledge of the chemical basis for schizophrenia (Nintey Fifth Congress, 1978). In 1987, the FDA removed Sernyl (phencyclidine's market name) from the human market and reserved it for use only as an animal tranquilizer, for which it is still used today (Peterson, 1978).

Unfortunately, some individuals were still able to obtain the drug, either through theft or home synthesis in a garage laboratory (Nintey Fifth Congress, 1978). It was distributed under a number of slang terms, including PeaCe Pill, THC, and Love Boat; and rapidly spread throughout the country as a result of its low price and availability (Peterson, 1978). There were many casualties. not because of the drug, but because of its effects.

Hospitals also noticed a sudden increase in paranoid schizophrenic admissions (Peterson, 1978), which naturally sparked more interest in this enigma of a drug, and raised many questions: Why were people addicted to a drug which seldom generated " good trips"? Why (and more importantly, how) was this drug causing episodes of paranoid schizophrenia? A new era in drug research for schizophrenia had been opened.

The Excitory Amino Acid Link If one takes a moment to consider what a amazing drug PCP is, then it is easy to see just why scientists were so excited. Here was a single chemical which could induce schizophrenia (Restak, 1994), a bright arrow pointing to a possible cause of this terrible disorder. Scientists hypothesized that perhaps there were naturally occurring phencyclidine-like substances within the brain which malfunction and caused psychotic states (Restak 1994).

This “ magic” compound was jokingly referred to as “ Angle Dustin” (Restak, 1994). In truth, these scientists were much closer to the truth than they thought. but there is an interesting twist. In the brain, there are three prevalent amino acid neurotransmitters: glycine, glutamate, and aspartate; collectively these are referred to as the excitory amino acids (Restak, 1994).

They are secreted at nerve terminals, and interact with receptors on the neuron at the post synaptic membrane (Haberstadt, 1995).

Without these neurotransmitters, the brain would simply cease to work. Too much of them, however, and the brain also tends to stop working. These neurotransmitters function by opening ion channels within a neuron, effectively depolarizing it; through “ coupling via the glutamate receptor with other chemicals that initiate a chain reaction of interlinked chemical processes within the neuron” (Haberstadt, 1995). In other words, they excite the neuron by allowing charged ions to enter it.

As said before, however, too much of these neurotransmitters would kill the neuron by exciting it to death. As a matter of fact, this is the principle damaging factor in stroke patients (Restak, 1994).

When a neuron dies, it releases copious amounts of amino acid neurotransmitters which then kill other brain cells through the excitotoxic effect (Souza, 1993). In order to study this effect more fully, scientists used a glutamate analog known as NMDA (N-methyl-D-Aspartate) which was considerably more potent than glutamate by itself (Souza, 1993). Quite accidentally, the scientists also discovered an NMDA antagonist, which turned out to be phencyclidine. Now here is an interesting situation: PCP is

known to be a “ bad” drug, causing many unwanted effects and hardly any beneficial ones.

NMDA (or more appropriately, the excitatory amino acids), on the other hand is a good drug; being necessary for normal brain functioning. Ironically, PCP is a N- methyl-D-Aspartate antagonist and counteracts any damage done by excitotoxic levels of NMDA in laboratory animals (Restak, 1994).

This is where a very important question is raised: What role do excitory amino acids play in schizophrenia? There are, of course, two possible directions to this question. Either schizophrenic patients have too much glutamate, or too little (Haberstadt, 1995). Unfortunately, the answer is never quite so simple; but some important pieces in the schizophrenia puzzle had been found (Haberstadt, 1995).

Biochemistry of an Angel For the last decade, scientists have been hard at work trying to decipher the complex biochemistry of PCP. The results have been extraordinary, with the effects of phencyclidine depending on a magnificent symphony of receptor sites and chemical concentrations on the neuron.

As was stated before, the effects of the excitory amino acids are mediated by the NMDA receptor subtype (in addition to 4 others) (Restak, 1995). It is known that one of PCP’s major preferences lies with the NMDA receptor complex (Souza, 1993). The NMDA receptor “ mediates ion flux through a channel permeable to Na+, K+, and Ca2+” (Souza, 1993).

The ion flux is voltage dependent, which is in turn controlled by Mg2+ and phencyclidine (Souza, 1993). On the other hand, the extent of channel activation is controlled by glycine through the use of NMDA agonists (Souza, 1993). Some polyamines have also recently been shown to use some sites to control glycine binding (Haberstadt, 1995). In addition, the NMDA and glycine receptors have been shown to exist in both antagonist and agonist conformations, depending on the relative concentrations of glutamate, glycine, and polyamine compounds (Haberstadt, 1995).

It is through this rather complex series of checks and balances that the effects of PCP are mediated.

In short, the effects depend on the extent of channel activation; which is dependent on at least five different receptor/binding sites. After considerable experimentation, the actual site of the PCP receptor was pinpointed as being within the actual channel gated by the NMDA excitory amino acid receptor (see figure 2. 0). There are several important points which support this conclusion.

Most obvious is that the “ PCP and NMDA receptors are co-localized in the central nervous system” (Souza, 1995). Second, the “ PCP receptor ligands have been shown to inhibit NMDA-receptor-mediated conductance non-competitively in a voltage and use dependent fashion” (Souza, 1995).

Lastly, the effectiveness of the PCP receptors is decreased by competitive NMDA receptor agonists but increased by competitive NMDA receptor antagonists (Souza, 1993), an exciting lead when it comes to determining the chemical mechanisms of schizophrenia, as related to a malfunction in

the NMDA receptor function. Since PCP inhibits the NMDA receptor, the schizophrenic brain’s NMDA receptors may be below normal functional parameters (Haberstadt, 1995). The Crazy Angel is Blamed There is no doubt that PCP induces a state very similar to positive symptom schizophrenia. There is some doubt, however, if PCP’s tendency to block the NMDA channel is to blame for the relevant clinical symptoms (Halberstadt, 1995).

The ability for the PCP molecule to bond with such effectiveness to the PCP receptor within the channel is certainly strong evidence, but some doubt the degree of blame. Fingers have also been pointed at the “ haloperidol-sensitive sigma” receptor sites, and at monoamine reuptake sites (the core of the dopamine hypothesis for schizophrenia) (Halberstadt, 1995). These alternative sites are also receptive to a PCP molecule, and undoubtedly play a role in schizophrenia, but several lines of evidence support the PCP receptor as the major force behind the “ psychotomimetic effects of PCP” (Svennson, 1995). First, “ PCP receptors have been shown to mediate the discriminative stimulus effects of PCP in rodents” (Svennson, 1995).

PCP researchers have trained animals to discriminate between PCP and saline solutions. When these animals are give one of a wide range of chemical substances (each from a distinctive chemical class), the animal’s response is directly proportional to the rank order of the drug’s binding power to the PCP receptor. Hence, a stronger PCP receptor bond leads to a better NMDA channel blockade, and a stronger drug response. On the other hand, there is no PCP-like result when the test animals are given drugs which selectively bind to sigma and/or dopamine reuptake sites (Svennson, 1995).

Second, “ psychotomimetic effects similar to those induced by PCP can be induced by ketamine, a related arylcyclohexamine derivative” (Sevvenson, 1995). This is a particulary strong point of evidence, especially when coupled with the following point: A dosage of ketamine ten times that of PCP is required in order to induce the same effect (Halberstadt, 1995).

This fits perfectly with ketamine’s reduced effectiveness in binding to PCP receptors, which is approximately ten times less than that of PCP. Ketamine is also “ essentially inactive” (Halberstadt, 1995) at both sigma receptor and dopamine reuptake sites.

At this time it is important to note that PCP does indeed also bind to sigma receptors and dopamine reuptake sites, albeit with a lower affinity (Okuyama, 1994). This may be an important functional link between schizophrenia and PCP; since ketamine binds only to PCP receptors and does not induce paranoid schizophrenia. PCP, on the other hand, has a broader receptor range and does induce schizophrenia (Halberstadt, 1995). Finally, there is consistent evidence that PCP psychosis can be induced by serum concentrations of 20 nM (Souza, 1993).

Any PCP levels which are higher than 400 nM are associated with anesthetic effects. It has been shown that PCP receptors bind to PCP at concentrations of 30-50 nM, “ suggesting a highly significant degree of receptor occupancy by levels of PCP present during low dose PCP psychosis” (Souza, 1993). This point is hammered home, considering that sigma binding and dopamine reuptake sites only bind to PCP along the order of 600 nM and 700 nM,

respectivly (Souza, 1993). It is easy to see that the affinity these sites have for PCP is significantly lower than that of the PCP receptor.

Hence, it is not very likely that the small amount of PCP needed for psychosis would be acting on anything except the PCP receptors. Once again, however, it is important to remember that PCP does not bind solely to PCP receptors.

Opposites Attract One of the prevailing theories of schizophrenia is the dopamine hypothesis, in which abnormal dopamine levels are implicated as its cause. This theory seems to conflict with the theory presented in this paper, in which abnormal functioning of the NMDA ion channel is seen as the cause.

There is, however, another important aspect of PCP induced psychosis which has not yet been discussed: the link to the A10 dopamine releasing neurons (Restak, 1994). Most of the brain’s dopamine is thought to be released from the A10- mesolimbic-mesocortical system within the ventral tegmental region of the brain (Halberstad, 1995). This area is thought to play an important role in addiction to PCP since PCP seems to stimulate the release of dopamine, a behavior enforcing mechanism (Halberstad, 1995).

How phencyclidine was is able to do this has remained a mystery until only recently.

It was previously unknown as to which receptor was more important in stimulating dopamine release, the PCP receptor or the sigma receptor (Halberstad, 1995). To find out, scientists gave test animals one of five PCP-receptor specific drugs; MK-801, PCP, (+)SKF, or ketamine (Restak, 1994).

The degree of A10 excitation was then measured. With MK-801 being the most powerful PCP ligand, a 40% increase in A10 neuronal firing rate is detected. Following closely behind are PCP, (+)SKF and ketamine, respectively (Restak, 1994). This order correlates perfectly with the respective order of PCP receptor binding, strong evidence in supporting the role of the NMDA ion channel in A10 dopamine release (Restak, 1994).

On the other end of the spectrum, giving test animals the potent sigma ligand (+)pentazocine resulted in only a 14% increase in A10 neuron firing rate (Halberstad, 1995), with DTG having no measurable effect (Halberstad, 1995). Moreover, A10 activation by PCP is not attenuated by haloperidol; which has the highest known sigma receptor affinity (Halberstad, 1995). In other words, “ The potency of PCP-like drugs to alter A10 activity was found to correlate positively with their affinity for the PCP receptor and consequently with their potency as NMDA agonists”. (Halberstad, 1995) The obvious conclusion to draw from the above research is to say that stimulation of the A10 neurons is the result of NMDA channel blockage.

In a strange twist however, this does not appear to be the case. The chemicals NPC 12626 and ()CPP are among the most potent NMDA channel blockers known (Souza, 1995).

When animals are given NPC 12626 or ()CPP there is no change in A10 firing rate, even after 45 minutes of infusion (Souza, 1995). If this treatment is then followed up by infusion with PCP, then the normal 40% increase in dopamine firing is noted. not a higher rate as would be predicted by the current model (Souza, 1995).

Obviously, NMDA channel blockage is not behind the increased A10 neuronal firing (Souza, 1995). The mechanisim by which PCP does induce this effect is still subject to research (Halberstad, 1995). Regardless, phencyclidine does have an effect on dopaminerginc activity and dopamine does play an important role in schizophrenia (Souza, 1995). From this, one can see that PCP agonists or antagonists may well be useful in treating schizophrenia. The Crazy Crazy Man When applying PCP psychosis to schizophrenia, a rather intriguing question arises: What effect would PCP have on schizophrenics.

The answer, of course, raises more questions than it answers.

According to Crow, there are two types of schizophrenics, Type I and Type II (Halberstad, 1995). Surprisingly, this model fits quite nicely when these patients are treated with PCP. Type I schizophrenics have a " super sensitive response to the normal amounts of endogenous PCP ligand" (Halberstad, 1995). Type II schizophrenics, on the other hand, show " Dysfunction of the feedback look regulating PCP ligand activity, resulting in excess PCP ligand levels" (Halberstad, 1995). Type I's response is the result of excess A10 dopaminergic activity which makes the PCP receptor considerably more sensitive (Halberstad, 1995).

Type II's response, the dysfunction of the feedback loop, " is analogous to hypthalmic-pituitary-adrenal (HPA) axis dysfunction in endogenous dysfunction (Halberstad, 1995). In general terms, a small dose worsens Type I but leaves Type II untouched (Halberstad, 1995). A larger dose of PCP worsens Type I to an even greater extent, while Type II shows moderate improvement (showing the amphetamine-like activity induced by PCP)

(Halberstad, 1995). From this data, it can be concluded that people who have a psychotic response to PCP have a “ biologic diathesis” (Restak, 1994) sensitivity to PCP resembling that which Type I patients exhibit; except with a diminished genotypic expression (Halberstad, 1995). Curing the Ill A number of novel drug treatment ideas have arisen from all the PCP research, the most obvious of which is a attempted treatment of schizophrenia by drugs which keep the NMDA channel open.

This is, however, more difficult than one would first expect. Direct stimulation on the channel is not possible, since neurotoxicity would result from excessive calcium ion levels within the neuron (Peterson, 1978). Instead, many of the current drugs call on glycine to stimulate the channel indirectly. Recall that glutamate is responsible for keeping the channel open, with help from certain reinforcing molecules like glycine and polyamines (PCP closes the channel, and causes psychosis).

In one experiment, 11 schizophrenic patients were given 5-25mg of glycine per day as “ a concomitant drug to the neuroleptic treatment” (Souza, 1993). Four of the initial eleven patients responded favorably to this, as would be expected. In a related open study, glycine was given to six chronic schizophrenic patients.

Two of the subjects benefited, one of which deteriorated when denied the drug (Souza, 1993). Two other patients actually worsened as a result of the treatment, while the remaining four showed no change (Souza, 1993). In another study, five male schizophrenic patients were given the pro- drug

known as Milacemide (Souza, 1993), which is an acetylated version of glycine.

Milacemide is better able to cross the blood brain barrier, as compared to pure glycine (Souza, 1993). Milacemide was given to five male schizophrenic patients after a three day medication free period (Souza, 1993). All of the subjects worsened, three of which could not complete the study due to increases suspiciousness, hostility, or agitation. The negative results, however, could have been the result of the 3 day drug free period preceding the test period (Souza, 1993).

Although no real benefit has been shown by the preceding treatments, the principle behind their action is still strong.

It has been suggested that tests be run on other glutaminergic drugs, like polyamines (Souza, 1993). The NMDA complex will probably be better stimulated by " direct glutamate agonists" (Halberstad, 1995), which we may be able to synthesize in the future without their neuron damaging effects. Regardless, we must not be dissuaded by these disappointing results. PCP does induce schizophrenia, and there must be a preventive or curative measure.

Conclusion It is ironic to think that a drug as terrible as phencyclidine could hold such incredible promise in cracking the mystery of schizophrenia.

Although that day may be far in the future, PCP research has already opened many new doors in other areas of neurologic dysfunction; such as in the treatment of epilepsy and stroke damage. PCP has already been shown to

have a number of good uses, If not anything else, this amazing substance has given us a fascinating look into the elegantly complex world of neurochemistry.

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