Table

Relative potencies (phencyclidine = 1)
A = rotarod test; B = specific receptor

Compound	Isomer†	A	B
N-(1-Phenyl-2-methyl-cyclohexyl)piperidine	cis	0.03	0.16
	trans	0.54	2.08
N-(1-(2-Thienyl)-2-methyl-cyclohexyl)piperidine	cis	<0.03	0.25
	trans	1.14	6.25
N-(1-Phenyl-4-methyl-cyclohexyl)piperidine	cis	0.73	1.92
	trans	<0.03	0.50

†cis or trans correspond to the relative position of substituant and aromatic in relation to the plane of cyclohexyl ring.

For each isomeric pair, the compound in which the conformation is most displaced towards the one with an axial phenyl gives the best score. Some of the most striking results are shown in the Table.

Considering for example N-(1-(2-Thienyl)-2-methylcyclohexyl) piperidine, the trans isomer is more than 25 times as potent in both tests as the cis isomer. Conformational studies had shown that in the former, the aromatic group is more axial than in the latter isomer. In other words, the binding to biological receptors of PCP and its derivatives most probably occurs in the thermodynamically most stable conformation with an axial phenyl group.

It can be concluded then that as a hypothesis for further experiments the axial aromatic structure is the most active one in the PCP series.

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Interdiscipinary Studies On Phencyclidine at the Addiction Research Center, Lexington, Kentucky

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In comparison with other classes of abused drugs, there have been unique concerns associated with the abuse of phencyclidine (PCP) and its numerous analogs. Much of this concern has centered upon the fact that these compounds are relatively easily synthesized and their synthesis can be accomplished by individuals with only modest technical training and without elaborate equipment. The "starting" chemicals are widely available, and because of their important industrial uses, do not lend themselves to more stringent controls. Thus, illicit chemists are af-

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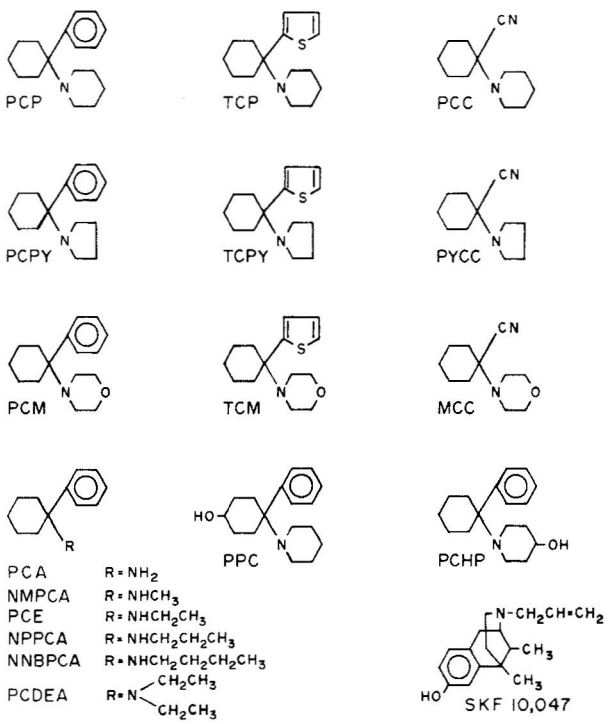
forded the opportunity to synthesize PCP analogs which are not subject to legal controls but may have the potential to be abused like PCP. For those compounds which have originated in illicit laboratories, no systematic data exist which may be used to evaluate their abuse potential and pharmacologic classification.

In response to these and other issues, an interdisciplinary research program was focused on PCP and related compounds in an effort to provide needed systematic data. Structures of some of the compounds studied are illustrated in the Figure. The objectives of this research program have included: 1) the development of analytic chemical methods for identifying PCP as well as its analogs and metabolites in biological samples; 2) systematic studies of the pharmacology of PCP, particularly in comparison with other drugs of abuse; 3) evaluation of PCP analogs and metabolites for purposes of drug classification; 4) evaluation of the abuse liability of PCP and its analogs; and 5) determination of the mode of action of this group of compounds.



Figure

Analytic chemical methods were developed for the identification of PCP analogs in biological samples (1). The most specific method for detecting the various PCP analogs was determined to be chemical ionization-mass spectrometry. These methods were applied to identifying metabolites of PCP in the urine of the dog, rat, and mouse. Although species differences in metabolism were observed, the primary metabolites excreted by all three species were the 4-hydroxypiperidine and 4-hydroxycyclohexyl metabolites. These metabolites were excreted primarily in conjugated form. Human urine also contained these two monohydroxy metabolites, again primarily in conjugated form.

In an effort to develop in vitro methods for assessing PCP analogs, the displacement by PCP analogs of specifically bound [^{3}H]-naloxone and [^{3}H]-PCP was investigated using the methods of Vincent et al. (2) and Zukin and Zukin (3). Micromolar concentrations of PCP analogs were required for displacing [^{3}H]-naloxone, although clear orders of relative potency were obtained which were significantly correlated with relative potencies for producing ataxia in the mouse and PCP-like discriminative stimuli in the rat. On the other hand, specific PCP binding in synaptosomal preparations occurred at nanomolar concentrations (ID50 = 270 nM). Clear orders of relative potency were also obtained for a large series of PCP analogs in displacing [^{3}H]-PCP. Two psychotomimetic opioid derivatives, cyclazocine and N-allylnormetazocine (SKF 10,047), also displaced specifically bound [^{3}H]-PCP. The relative potencies of these compounds for displacing [^{3}H]-PCP were only poorly correlated with their relative potencies for producing ataxia in the mouse and PCP-like discriminative stimuli in the rat. Thus, the interpretation of these latter binding data is uncertain. However, since binding serves as a measure of affinity and not intrinsic activity, it is possible that there are marked differences in intrinsic activity among these PCP analogs which may account for the apparent discrepancies among relative potencies. Further pharmacologic data are needed to test this hypothesis. In addition, metabolism and/or lipid solubility may play integral roles in determining the in vivo potency of these PCP analogs, while such factors do not contribute to their potencies in the binding assays.

Several dog preparations were utilized to assess the whole animal pharmacology of PCP. In the chronic spinal dog, the dose-related effects of PCP included depression of the flexor reflex, tachycardia, mydriasis, retraction of the nictitating membrane, increased latencies of the skin twitch and pupilloconstrictor reflexes, and hyperthermia. While the dogs remained essentially quiet, their behavior was characterized further by nystagmus, staring or tracking eye-movements, stereotypic head movements, salivation, and opistotonic posturing. This profile of effects is readily distinguishable from the profiles produced by

prototypes of other classes of abused drugs, but closely resembles the profile produced by the psychotomimetic opioid N-allylnormetazocine. Self-administration behavior was also readily maintained by response-contingent intravenous infusions of PCP and ketamine in the dog. The number of infusions self-administered during daily sessions was inversely related to the amount of drug delivered per infusion; thus, for each drug, total drug intake per session remained relatively constant. A comparison of the dose-response functions for the two drugs indicated that ketamine is approximately one-fifteenth as potent as PCP with regard to maintaining equal rates of drug-reinforced responding. EEG studies in the unrestrained dog demonstrated that PCP and ketamine caused behavioral excitation and EEG activation. Both drugs produced low amplitude, high frequency (< 15 Hz) patterns in the parietal and occipital cortices, while continuous theta activity was observed in the hippocampus. These amphetamine-like EEG actions of PCP in the dog differ from those reported in humans and cats.

Additional pharmacologic studies were conducted in the mouse and rat. In the mouse, ED_{50} values for producing ataxia as measured by the rotarod as well as LD50 values were determined for a large number of PCP analogs and carbonitrile synthetic intermediates. In producing ataxia, the 1-phenylcyclohexyl-monoalkylamines were among the most potent compounds tested. On the other hand, the carbonitrile compounds were determined to have the lowest LD50 values as well as the lowest $LD50/ED_{50}$ ratios. In the rat, the discriminative stimulus properties of PCP and a large series of analogs were evaluated as an animal model for the subjective effects these drugs produce in man. Rats trained to discriminate between saline and PCP identify a number of PCP analogs as being PCP-like, including the 4-hydroxypiperidine metabolite and all analogs thus far identified in street drug samples. Among drugs which the rats did not identify as being PCP-like were the carbonitrile precursors, the 4-hydroxycyclohexyl metabolite, and several prototypic drugs from other classes including amphetamine, morphine, LSD, ketocyclazocine, and pentazocine. However, the rats did generalize between PCP and the psychotomimetic opioid derivatives N-allylnormetazocine and cyclazocine. Further, results from these drug discrimination data indicated that substitutions on the N-atom were not required for PCP-like activity, whereas modifications of the cycloalkyl ring consistently reduced PCP-like activity.

From these interdisciplinary studies, several conclusions may be drawn concerning the pharmacology and potential abuse liability of PCP and its analogs. First, PCP appears to represent a class of drugs distinct from other classes of abused drugs, although it may have either similar physiologic actions or common mechanisms of action with at least some psychotomimetic opioids. Second, structure-activity relationship data indicated that an electron dense region in the area of the aromatic ring of PCP and the cyclohexyl moiety of PCP are required for producing PCP-like activity; substitutions on the nitrogen atom, however, are not required. Third, contrary to previous reports (4,5), the two monohydroxy metabolites of PCP are biologically active and probably contribute substantially to the overall spectrum of action of PCP. And fourth, behavioral experiments have demonstrated that several of the PCP analogs that produce PCP-like discriminative stimuli are also self-administered. When taken together, the results of these two behavioral methodologies appear to be predictive of drugs which may have a PCP-like abuse potential in man.

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Clinical and Laboratory Diagnostic Problems With Phencyclidine (PCP) Toxicity

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Since most alkaloid agents have psychoactive potential and more than 5,000 plants are alkaloidal, it is rather surprising that we do not have more psychiatric compounds in use at any one time. Unfortunately, at the present time, the fad drug called phencyclidine (PCP) is difficult to measure in a routine laboratory and causes

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