chromes with various xenobiotics, the effects of phencyclidine (PCP) were examined. The formation of a reactive iminium ion from PCP, as well as the covalent binding of PCP metabolites to proteins and the inhibition of N-demethylase activity in the microsomal system by PCP have previously been reported by others (Hoag, M. K. P., A. J. Trevor, Y. Asscher, J. Weissman and N. Castagnoli. *Drug Metab Disp* **12:** 371–375, 1984. Ward, D. P., A. J. Trevor, A. Kalir, J. D. Adams, T. A. Baillie and N. Castagnoli. *ibid.* **10:** 690–695, 1982). We have found that PCP selectively inactivates P-450 form 2, the major phenobarbital-inducible isozyme from rabbit liver microsomes, in a reconstituted system containing NADPH-cytochrome P-450 reductase, phosphatidylcholine, and an NADPH-generating system. Aliquots were taken over time from this mixture, diluted 20-fold, and assayed for 7-ethoxycoumarin deethylase activity, Time-, NADPH-, and PCP concentration-dependent inhibition of deethylase activity were observed. The kinetics are indicative of a biphasic first order process with rate constants of 0.43 and 0.07 min^{-1} for the fast and slow phases, respectively. The iminium intermediate (kindly provided by Drs. Hoag, Trevor, and Castagnoli) also inactivated isozyme 2 at a similar rate, but was less selective, for it also inhibited constitutive cytochrome P-450, form 3b. PCP and the iminium ion had little or no effect on ethanol-inducible P-450 form 3a, 3-methylcholanthrene-inducible form 4, or tetrachlorodibenzo-*p*-dioxin-inducible form 6. PCP caused little or no change in P-450-mediated activities in intact microsomes, due mainly to the presence of P-450s other than form 2; furthermore, titration with anti-form 2 antibody of the residual microsomal activity after PCP treatment indicated that no other forms were affected. The loss of the Soret absorption band and of the ability to form the ferrous carbonyl complex and the pyridine hemochrome complex indicates modification of the heme moiety. Experiments are in progress with tritiated PCP to elucidate further the nature of its interaction with P-450 heme and apoprotein. (Supported by NIH grant DK-10339.)

MOLECULAR CRITERIA FOR AN IMMUNOLOGICAL MODEL OF THE PCP RECEPTOR. Owens, S. M., M. Zorbas, M. Gunnell, M. Polk and D. L. Lattin. Department of Pharmacology and Interdisciplinary Toxicology and Department of Biopharmaceutical Sciences, University of Arkansas for Medical Sciences, Little Rock, AR 72205.

A series of antibodies against PCP derivatives were generated in rabbits to determine the molecular requirements for an immunological model of the PCP receptor. Three different antibodies were produced against the PCP molecule by immunization with haptens covalently bound to bovine serum albumin (BSA) off of the para position of each of the three ring structures of PCP (i.e., aromatic, cyclohexane and piperidine rings). A fourth antibody was produced by immunization with BSA coupled to the PCP metabolites, PCHAP (5-[N-(1'-phenylcyclohexyl)amino]pentanoic acid). The antigen for this fourth antibody was designed to produce antibodies that would be highly cross-reactive with the potent PCP analogue, PCE (N-ethyl-1-phenylcyclohexylamine). The cross-reactivity patterns of all four antibodies were then determined in a radioimmunoassay (RIA) format using ^{3}H-PCP and numerous PCP analogues. The relative potencies of these antibodies, determined from IC_{50} values, were then correlated with relative potency data from receptor binding studies (Quirion *et al.*, 1983) and from discriminative stimulus studies in the rat (Shannon, 1981). There was a significant correlation between the PCHAP RIA data and the receptor binding data ($r=0.89$; $p<0.005$), and between the PCHAP RIA data and the discriminative stimulus data ($r=0.89$; $p<0.005$). Since none of the other antibodies showed any correlation with the relative potency data from receptor binding or behavioral studies, the PCHAP antibody appears to be the best immunological model for the PCP receptor. In related studies, the antigens used for the production of the antibodies were used as ligands in a ^{3}H-PCP neuroreceptor binding assay. The PCHAP antigen was found to be the most potent antigen for inhibition of ^{3}H-PCP binding. These studies represent preliminary evidence that an immunological model can be developed for the PCP neuroligand binding site. (Supported by NIDA grant DA 04136 and NIDA Research Scientist Development Award (S.M.O.) KO2 DA00110.)

EFFECTS OF PHENCYCLIDINE HYDROCHLORIDE ON NEUROENDOCRINE FUNCTION IN THE RAT. Pechnick,* R. N., R. George* and R. E. Poland.† *Department of Pharmacology, U.C.L.A. School of Medicine, Los Angeles, CA 90024; and †Division of Biological Psychiatry, Harbor-U.C.L.A. Medical Center, Torrance, CA 90502.

Phencyclidine (PCP) is a widely used drug of abuse; however, little is known of the effects of PCP on neuroendocrine function. We have previously reported that the acute administration of PCP produced increased serum levels of corticosterone in the rat (*Life Sci* **38:** 291–296, 1986), but it is not known whether this effect is due to a direct effect on the adrenal or is mediated via increased release of adrenocorticotrophin (ACTH) from the pituitary. The purpose of the present study was to determine the effects of the acute administration of PCP on the release of ACTH, and in addition, luteinizing hormone (LH) in the rat. Male rats were injected SC with saline or varying doses of PCP, and trunk blood was obtained at 15, 30, 60, 120, and 180 min after injection. Plasma levels of ACTH and LH were measured by radioimmunoassay. PCP increased plasma levels of ACTH 15 min after administration, and ACTH levels remained significantly elevated 180 min after injection with the higher doses. In contrast, PCP decreased serum levels of LH; however, this effect was not observed until 180 min after injection. These findings indicate that PCP is a potent releaser of ACTH but inhibits the release of LH in the rat. (Supported by NIDA grant DA-04113.)

EVIDENCE FROM 2-DG AUTORADIOGRAPHY THAT PHENCYCLIDINE'S FUNCTIONAL EFFECTS ARE MEDIATED BY SPECIFIC PCP RATHER THAN SIGMA RECEPTORS. Piercey, M. F., C. Ray and G. D. Vogelsang. CNS Research, The Upjohn Company, Kalamazoo, MI 49001.

Sokoloff's 2-deoxyglucose (2-DG) autoradiographic technique (*J Neurochem* **28:** 897, 1977) was used to identify neural structures underlying the behavioral effects of phencyclidine (PCP) and to compare the distribution of PCP's

functional effects to the distribution of specific 'PCP' and sigma receptors, both of which bind PCP (Vignon *et al., Brain Res* **378:** 133, 1986). PCP, 5 mg/kg, was administered IP to male Sprague-Dawley rats 15 min prior to 25 μCi IV (^{14}C)-2-DG. Animals were sacrificed 45 min later. Autoradiograms of coronal sections were prepared from prefrontal pole to cervical cord. Computerized image analysis yielded quantitative measurements of regional energy metabolism. PCP dramatically increased metabolism in discrete brain regions, nearly all of which were located in diencephalic and telencephalic structures rich in PCP receptors (Largent *et al., JPET* **238:** 739, 1986). These effects were greatest in the limbic circuit described in 1937 by Papez (mammillary bodies, anterior thalamus, cingulate gyrus, entorhinal cortex, hippocampus, fornix), which was dramatically excited throughout, and the terminal zones of dopaminergic projections (caudate, n. accumbens, olfactory tub., prefrontal cortex). In general, anterior cortical regions, (especially sensory-motor cortex), were only weakly stimulated or even depressed, compared to more caudal cortical zones, (particularly striate 18), giving rise to an anteroposterior gradient similar to that reported in schizophrenia. Brainstem areas rich in sigma receptors (Largent *et al., ibid)* were generally unaffected. The inferior colliculus and the lateral habenula were inhibited. Chi-square analysis revealed a strong positive correlation for the areas stimulated with the presence of PCP receptors and a negative correlation with the presence of sigma receptors. Stimulated areas lacking PCP receptors (mamm. bodies, SNPR) had strong neuronal links to areas having high levels of PCP receptors. Haloperidol (HAL), which binds to sigma but not PCP receptors, antagonized PCP's stimulant effects in most dopaminergic areas, but not in Papez' circuit. Even HAL's effects were negatively correlated with the presence of sigma receptors. HAL tended to depress PCP's cortical stimulation throughout without altering the anteroposterior gradient; indeed, some anterior cortical regions were severely depressed below controls. HAL did not significantly affect PCP's intense cingulate stimulation. Although HAL stimulated the lateral habenula, it only partially reversed the depression evoked by PCP. It is concluded that PCP elicits its extreme psychotropic effects by intense stimulation of Papez' limbic circuit and dopamine release, all of which are probably mediated either directly or indirectly through the PCP receptor.

QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP MODEL FOR PHENCYCLIDINE (PCP) COMPOUNDS. Pirat,* J. L. and J. M. Kamenka. Laboratoire de Chimie Organique Physique Appliquée and LP 8402-U 249, Ecole Nationale Supérieure de Chimie, 8, rue de l'Ecole Normale, Montpellier Cédex-France; Arnone, M. and M. Morre. Sanofi Recherche, Toulouse, France.

From previous results in our laboratory and others, modifications on the aromatic ring of the PCP molecule appear to influence biological activity *in vitro* and *in vivo*. Additionally, substitutions on the cyclohexyl moiety could contribute to an increase in PCP-like properties. To test this hypothesis, a model equation was generated for a structure with an intact phenyl group using the following parameters: steric-crowding (length), lipophilicity (Rekker's parameter), conformation and affinity for the ^{3}H-PCP receptor. This chemical model N-(phenyl-3,4-dimethylcyclohexyl) piperidine *cis* [2] was synthesized and tentatively improved by aromatic and piperidinic substitutions by a synthetic pathway to [2] via a classical Bruylants reaction on the suitable nitrile compound. Surprisingly we obtained stereoisomeric pairs although the Bruylants reaction has been generally regarded as stereospecific. Thirty new compounds were isolated and their structure characterized by ^{13}C NMR. Their binding properties were tested in competition with ^{3}H-PCP on guinea pig brain membranes. Few compounds exhibited affinities in the range of that for PCP. The mouse rotarod test did not show typical ED_{50}/IC_{50} relationships. The ED_{50} values were generally much higher than expected. However, behavioral evidence for antagonist properties was not found. Although the molecules obtained are related to PCP at the molecular level they seem to be devoid of agonist or antagonist properties in the behavioral test. It can be concluded that the cyclohexyl ring may play a role in the modulation of the biological activity of the PCP structure but not in the specific enhancement of PCP-like activity. *Present address: Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109-0626.

PHENCYCLIDINE AND NMDA—GLUTAMATE RECEPTORS IN HUMAN BRAIN. COMPARATIVE CHARACTERIZATION IN HUMAN BRAIN BIOPSIED TISSUES. Quirion, R., M. Dalpe, S. Lal, A. Olivier and M. Avoli. Douglas Hospital Research Centre and Montreal Neurological Institute, McGill University, Verdun, Quebec, Canada H4H IR3.

Much recent evidence has suggested that one class of glutamate receptor sites, namely the N-methyl-D-aspartic acid (NMDA) type, are closely associated to phencyclidine (PCP) receptors. Interestingly, it has recently been shown that both NMDA and PCP receptor sites are decreased in similar fashion in certain brain regions in Alzheimer's Disease (Maragos *et al., Trends Neurosci* **10:** 65–68, 1987). This supports the hypothesis of a close association between PCP and NMDA receptor sites and suggests possible involvement of these systems in the pathophysiology of Alzheimer's Disease. However, another study has shown that PCP and NMDA binding sites are only decreased in a sub-group of advanced Alzheimer patients (Monaghan *et al., Neurosci Lett* **73:** 197–200, 1987. This could be related to the different protocols used to characterize NMDA receptor type. Additionally post-mortem delays could generate certain artefacts that would be difficult to dissociate from the disease. To investigate this possibility, we report here on the comparative quantitative autoradiographic distribution of PCP and NMDA receptor binding sites in fresh human cortical biopsied tissues obtained following surgical removal in epileptic patients. Temporal cortex (outside epileptic foci) was obtained following partial lobectomy in few male epileptic patients between 35–50 years of age. The tissue was maintained once following surgery and then frozen on dry ice and kept at −70°C until used for quantitative autoradiography. On the day of the experiments, 20 μm thick adjacent brain cortex sections were incubated in presence of various concentrations of [^{3}H] TCP (Contreras *et al., Neurosci Lett* **67:** 101–106) or [^{3}H] L-glutamate (first series according to Monoghan *et al., Brain Res* **340:** 378–386, 1985; second series according to Maragos *et al., Eur J Pharmacol* **123:** 173–174, 1986) exactly as described before. Our results show that [^{3}H]