STUDIES ON INHIBITION OF PHENCYCLIDINE-INDUCED HYPERACTIVITY BY GLYCINE. Toth, E. Center for Neurochemistry; Nathan, S. Kline Institute for Psychiatric Research, Ward's Island, New York, NY 10035.

We found recently that glycine inhibits phencyclidine (PCP)-induced hyperactivity without affecting the cerebral uptake of PCP in mice (Toth, E. and A. Lajtha, *Neurochem Res* **11**: 393–400, 1986). Since the latter is an indication of central effect, the possible mechanism of the inhibitory action of glycine was investigated. A single dose of glycine (50 μmol/g) that suppressed 75% of the hyperactivity induced by 5 μg/g PCP seemed to have no effect on the metabolism and binding of PCP. The amount of chloroform-extractable and particulate-bound radioactivity of the whole brain homogenates was similar in the glycine treated animals to that of controls after 10 min and 20 min following the administration of ^{3}H-PCP. The glycine had no significant effect on regional distribution of the drug in olfactory bulb, frontal cortex, lateral cortex, midbrain, pons-medulla, and cerebellum. It also did not affect the cerebral metabolism and the binding of PCP in vivo. Glycine affected the subcellular distribution of PCP. There was a reduction in radioactivity following the injection of ^{3}H-PCP (0.02 μCi/g) in the mitochondrial and microsomal fractions of the whole mouse brains by 30% and 40% respectively. The inhibitory effect of chlorpromazine on PCP-induced hyperactivity was greatly enhanced by glycine. Following the glycine treatment of mice, there was an increase in cerebral glycine and glutamine (100% and 80%) and a decrease in aspartate, glutamate, and taurine (10–20%). PCP (5 μg/g) had no effect on the level of neurotransmitter amino acids. The binding of spiroperidol in vivo was reduced 50% by glycine in the brains. It is suggested that the mechanism of inhibition of PCP-induced hyperactivity by glycine involves: (1) alteration in level of amino acid neurotransmitters, (2) alteration in the subcellular distribution of PCP, and (3) effect on the central dopaminergic system. It is possible that glutamine mediates the inhibitory action of glycine since both chlorpromazine and glycine increase cerebral glutamine levels and enhance each other's inhibitory action on PCP-induced hyperactivity in mice.

PHENCYCLIDINE METABOLISM: INVOLVEMENT ON IMINIUM ION INTERMEDIATES IN COVALENT BINDING, SUICIDE INACTIVATION OF CYTOCHROME P-450 AND FORMATION OF A NOVEL METABOLITE. Trevor, A. J., M. P. K. Hoag, M. Schmidt-Peetz and N. Castagnoli, Jr. Division of Toxicology, Departments of Pharmacology and Pharmacy, University of California, San Francisco, CA 94143.

The 1-(1-phenylcyclohexyl)-2,3,4,5-tetrahydropyridinium species (PCP-Im+) is a major metabolite formed from phencyclidine (PCP) during its cytochrome P-450-dependent oxidation by liver tissues. Nucleophilic "trapping" of PCP-Im+ with cyanide ion prevents the metabolism-dependent covalent binding of radiolabelled PCP to liver macromolecules and the mechanism-based inactivation of cytochrome P-450 by PCP. Synthetic PCP-Im+ added to liver microsomes inactivates cytochrome P-450 and the radiolabelled compound binds irreversibly to microsomal components. Both processes require further metabolism of the intermediate. The mechanism-based inactivation of cytochrome P-450 by PCP and PCP-Im+ is enhanced by pretreatment of rodents with phenobarbital. Selectivity of this inactivation for phenobarbital-inducible isozymes of cytochrome P-450 has been shown using purified forms of the enzyme (M. Coon *et al.*). Incubation of PCP-Im+ with liver microsomes in air plus NADPH has led to the isolation and characterization of 1-(1-phenylcyclohexyl)-2,3-dihydro-4-pyridone as a primary metabolite, the structure of which was confirmed by synthesis. This 4-electron oxidation product of PCP-Im+ is likely to occur via formation of a 2-electron intermediate, possibly the allylic alcohol, which also would be expected to undergo spontaneous dehydration to form reactive dihydropyridinium species. These metabolic transformations will be discussed in terms of the bioactivation of PCP to potentially toxic products. (Supported in part by NIDA grant DA 3405.)

^{18}F-PCP ANALOGS FOR POSITRON EMISSION TOMOGRAPHY (PET). Van Dort, M. E., D. J. Yang, M. R. Kilbourn, D. J. Gole, A. Kalir, D. C. Chu, A. B. Young, E. F. Domino and D. M. Wieland. University of Michigan Medical Center, Ann Arbor, MI 48109; and Tel Aviv University, Tel Aviv, Israel.

Glutamate receptors have been classified into various, subtypes of which the N-methyl D-aspartate (NMDA) receptor is of special interest. Drugs such as phencyclidine (PCP) and a PCP analog TCP bind either to an allosteric NMDA site or possibly to the ion channel itself. These recent findings have created a renewed interest to find a PCP-like compound for mapping NMDA-linked glutamate receptors in the human brain by PET. ^{18}F- and ^{11}C-labeled analogs of PCP are being investigated in our laboratories as possible probes for imaging NMDA type glutamate receptors in brain. Structural modifications by the introduction of substituents on either the cyclohexyl, piperidine or phenyl rings of PCP (1) leads to compounds with varying degrees of PCP-like activity. The relative potencies of some of these PCP analogs were determined *in vivo* in mice using motor coordination assessed by the platform test. In general, it was observed that substitution of either the cyclohexyl or piperidine rings resulted in a compound having lower PCP-like activity, probably due to a lower affinity of these molecules to receptor sites. Substitution on the phenyl ring either decreased or increased PCP-like behavioral activity depending upon the nature of the substituent and its position on the phenyl ring. The ED_{50} of PCP given IP in the mouse platform test was 19.7 μmol/kg. Substitution of either -OH or -NH_2 at the *m* position on the phenyl ring resulted in compounds with high potency and substitution of halogens in the *p* position resulted in compounds with relatively low potency. The ED_{50}s of *m*-OH, *m*-NH_2 (2) and *p*-Cl were 7.66 μmol/kg, 4.55 μmol/kg and 26.8 μmol/kg, respectively. Compound 3 with a -F atom in the *p* and -NH_2 group in the *m* position still retained its high potency (ED_{50} 4.48 μmol/kg). Using ^{3}H-TCP and rat brain homogenate, competitive binding studies are in progress with compounds 1–3. Preliminary studies have shown that reaction of 4 with ^{18}F-fluoride in DMSO at 160°C provides the respective ^{18}F analog 5 in an approximately 15% radiochemical yield as determined by radio-HPLC. Rapid reduction of 5 to 6 and further optimization of the ^{18}F-labeling reaction are under study.