PHENCYCLIDINE AND CEREBRAL CYTOCHROME P-450. Minn, A., B. Walther, R. Perrin, J. F. Ghersi-Egea, J. M. Ziegler and G. Siest. Université de Nancy I, Centre du Médicament, U.A. CNRS No. 597, 30 rue Lionnois, 54000 Nancy, France.

The cytochrome P-450 linked monooxygenase system (P-450) is responsible for the NADPH-dependent oxidation of a wide variety of lipophilic xenobiotics and endogenous substrates. Previous studies indicated that PCP undergoes extensive biotransformation in the liver with major group of metabolites derivated from aromatic hydroxylation and opening of the piperidine ring, these reactions being the result of P-450 activity (Kalir *et al.*, 1983). We recently showed that cerebral P-450 is mainly localized in mitochondrial and microsomal fractions (Walther *et al.*, 1986). Although cerebral P-450 activity is relatively low, the cerebral drug metabolism may be of importance in the production of toxic or reactive metabolites and possibly in the formation of peculiar pharmacologically active molecules. When substrates, products or inhibitors interact with the active site of P-450, typical difference spectra occur. The incubation of PCP with brain mitochondrial or microsomal P-450 promoted a "type I" spectral modification, indicating that PCP interacts with the active site as a substrate for this enzyme. On the other hand, when PCP was added to brain microsomes incubated in the presence of NADPH, some hydroxylated metabolites may be identified in the incubation medium. These results support the possibility of a cerebral biotransformation of PCP. As the administration of various drugs to animals causes selective induction of one or two particular forms of P-450 depending on the drug administered and leading to the activation of drug metabolism, we studied the effect of a chronic PCP treatment (25 mg/kg daily IP, 7 days) on the brain enzyme levels. No significative changes in microsomal nor mitochondrial P-450 levels were observed in these conditions. Kalir, A., A. J. Trevor, D. P. Ward, J. D. Adams, T. A. Baillie and N. Castagnoli. Reactive metabolites of phencyclidine and covalent binding to microsomal proteins. In: *Phencyclidine and Related Arylcyclohexylamines: Present and Future Applications*, edited by J. M. Kamenka, E. F. Domino and P. Geneste. Ann Arbor: NPP Books, pp. 267–277, 1983. Walther, B., J. F. Ghersi-Egea, A. Minn and G. Siest. Subcellular distribution of cytochrome P-450 in the brain. *Brain Res* **375:** 338–344, 1986.

PROPERTY OF PHENCYCLIDINE AS A 5-HT_2 RECEPTOR AGONIST. Nabeshima, T., K. Ishikawa, K. Yamaguchi, H. Furukawa* and T. Kameyama. Department of Chemical Pharmacology and *Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Meijo University, Nagoya 468, Japan.

Phencyclidine (PCP)-induced stereotyped behaviors including head-weaving, turning and backpedalling are mediated by serotonergic neurons, since the lesion of the striatum induced by a serotonergic neurotoxin, 5,6-dihydroxytryptamine, and the electrolytic lesion of the raphe nucleus which contains 5-HT cell bodies diminish PCP-induced behaviors (Nabeshima *et al.*, *Eur J Pharmacol* **91:** 455, 1983; ibid. **93:** 229, 1983). PCP interacts with the 5-HT_2 receptors, since it inhibits [3H]spiperone binding to 5-HT_2 receptors (Nabeshima *et al.*, *Res Commun Subst Abuse* **5:** 81, 1984; ibid. **5:** 175, 1984) and chronic administration produces down regulation of 5-HT_2 receptors (Nabeshima *et al.*, *Eur J Pharmacol* **109:** 129, 1985; ibid. **133:** 319, 1987). Methysergide inhibits the development of tolerance to PCP-induced head-twitch response, but not to head-weaving, turning and backpedalling. Methysergide protects [3H]ketanserin binding sites from the down regulation (Nabeshima *et al.*, *Eur J Pharmacol* **133:** 319, 1987). Furthermore, methysergide produces a precipitated withdrawal syndrome in PCP-tolerant rats (Nabeshima *et al.*, *Neurosci Lett* **69:** 275, 1986). Ritanserin, a selective 5-HT_2 receptor antagonist, antagonized the PCP-induced head-twitch responses in mice and rats (Nabeshima *et al.*, *Neurosci Lett*, in press, 1987). In the present experiments, we investigated whether PCP could protect the binding sites of [3H]PCP and [3H]ketanserin from an inhibitory effect of protein-modifying reagents which affect sulfhydryl groups. In the rat brain synaptic membrane, PCP (10 μM) provided a protection against inactivation of [3H]PCP and [3H]ketanserin binding sites induced by sulfhydryl reagents such as N-ethylmaleimide (NEM), iodoacetamide, 5,5'-dithiobis-(2-nitrobenzoic acid) and *p*-chloromercuribenzoate. Ritanserin (1 μM) also completely prevented the inhibitory action of NEM on [3H]PCP and [3H]ketanserin binding sites, but 5-HT (10 μM) failed to prevent it. 5-HT protected [3H]5-HT binding sites from the inactivation by NEM, but PCP and ritanserin did not show any effect. Scatchard plots of specific [3H]PCP and [3H]ketanserin binding showed that NEM (100 μM) caused a significant decrease in Bmax without changing Kd. Furthermore, PCP (10 μM) and ritanserin (1 μM) antagonized the decrease of [3H]PCP and [3H]ketanserin binding sites induced by NEM (100 μM). On the basis of the present findings, it is concluded that PCP has an ability as an agonist for 5-HT_2 receptors, and PCP binding sites overlap 5-HT_2 receptors. This work was supported in part by the Science Research Promotion Foundation of Japan Private School Promotion Foundation (#1986-11).

KETAMINE REDUCES NEUROLOGIC DEFICIT FOLLOWING 10 MINUTES OF CARDIAC ARREST AND RESUSCITATION IN CANINES. Natale, J. E., R. J. Schott and L. G. D'Alecy. Departments of Physiology and Surgery, The University of Michigan Medical School, Ann Arbor, MI 48109.

Ketamine HCl has been shown to minimize the acute excitotoxic action of glutamate on neuronal cells by non-competitive antagonism of the N-methyl-D-aspartate receptor. The augmented release of glutamate during ischemia leads to cell death due to excessive excitation in the midst of metabolic compromise. Ketamine was administered to canines following 10 minutes of cardiac arrest and resuscitation to determine whether ketamine administered following the arrest would attenuate ischemia-induced neurologic damage. Adult, male mongrel dogs (15–25 kg) were randomly assigned to either the ketamine treatment or vehicle control (0.9% NaCl) condition. During ventilation with 1.5% halothane and oxygen, catheters were introduced into the deep femoral artery and vein and jugular vein, and a left thoractomy was performed to expose the heart. Halothane and oxygen were replaced with room air ventilation. When