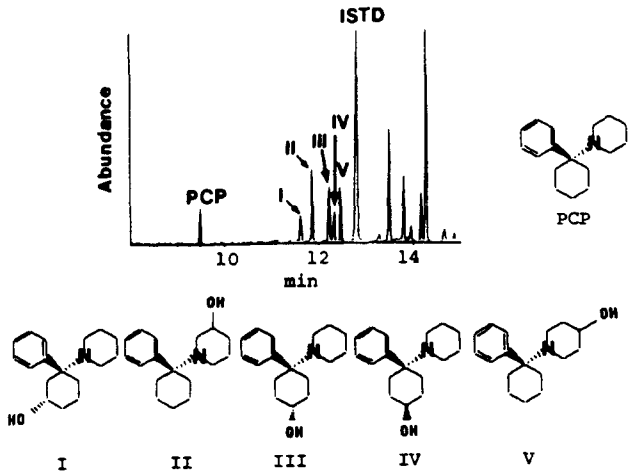
matography-mass spectrometry (GC-MS) procedure was developed to identify PCP, its major metabolites, other PCP analogs and derivatives. The method described is able to separate *m*-OH, *p*-OH, 3-OH pip (II), 4-OH pip PCP (V) and the stereoisomers of 2-OH cyclo, 3-OH cyclo and 4-OH cyclo PCP (III,IV). A sensitive and specific quantitative method was also developed to measure some of these monohydroxy substituted metabolites of PCP from biological samples. The method is based on a two step extraction of PCP related basic metabolites in an organic solvent followed by GC separation and mass selective detection of the extract derivatized with N,O *bis* (trimethylsilyl) trifluoroacetamide. The detection limit of the method was about 5 pmol per injection with a linear standard curve to 3 nmol. The assay was used for the quantitation of monohydroxy metabolites in the urine of PCP-dosed mice and rats. A typical chromatogram of the separation of various PCP metabolites in mice urine is shown below with the labelled peaks identified and remaining peaks unidentified. The 3-CH_2OH pip PCP served as the internal standard (ISTD). The *in vitro* biotransformation of PCP by mouse and rat liver microsomes was also studied. The presence of a recently identified metabolite, *trans* 3-OH cyclo PCP (I), was confirmed. A new metabolite, 3-OH pip PCP (II) was identified and quantitated in the urine and liver microsomal preparations. (Supported in part by NIDA grant DA 1531.)



BINDING STUDIES IDENTIFY TWO CLASSES OF PHENCYCLIDINE (PCP) RECEPTORS IN RAT BRAIN. Haring, R., Y. Kloog and M. Sokolovsky. Laboratory of Neurobiochemistry, Department of Biochemistry, The George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv 69978, Israel.

Binding experiments were employed in order to differentiate between PCP-receptor sites in rat brain. Two classes of PCP receptors were characterized and localized: one binds [^{3}H]-N-[1-(2-thienyl-cyclohexyl]piperidine ([^{3}H]TCP) with high affinity (K_d=10–15 nM) and the other binds the ligand with a relatively low-affinity (K_d=80–100 nM). The neuroleptic drug haloperidol did not block binding either to the high- or to the low-affinity [^{3}H]TCP sites whereas Ca^{2+} inhibited binding to both. Monovalent ions (K^+ or Na^+) selectively inhibited binding of [^{3}H]TCP or of [^{3}H]PCP to the high affinity sites, via an allosteric mechanism, resulting in the conversion of the high affinity sites to a lower affinity state, which is indistinguishable from the preexisting low affinity site. The two classes of [^{3}H]TCP binding sites have different patterns of distribution. Forebrain regions are characterized by high-affinity sites (hippocampus > frontal cortex > thalamus > olfactory bulb > hypothalamus) but some parts (e.g., hippocampus, hypothalamus) contain low-affinity sites as well. In the cerebellum and in the brainstem only low-affinity sites were detected. Binding sites for [^{3}H]PCP and for its photolabile analog [^{3}H]azido-PCP showed a regional distribution similar to that of the [^{3}H]TCP sites. The results are compatible with the existence of two classes of PCP receptors in the rat brain with a selective localization in the brain. (Supported in part by NIH Grant DABB IR01 DAO4168-01).

ETHYLKETOCYCLAZOCINE (EKC) ANTAGONIZES PHENCYCLIDINE (PCP)-INDUCED STEREOTYPED BEHAVIORS BY REDUCING MONOAMINE RELEASE. Hiramatsu, M., T. Nabeshima, H. Furukawa and T. Kameyama. Department of Chemical Pharmacology and *Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Meijo University, Nagoya 468, Japan.

Administration of PCP to rats induces a complex syndrome of behaviors such as hyperactivity, stereotypy and ataxia and it has been demonstrated that these behaviors are mediated via various neuronal systems. It has been suggested that the psychotomimetic effects of PCP are mediated by PCP/sigma receptors and that the psychotomimetic effects of opiates such as SKF 10,047 also reflect influences of the interaction of PCP/sigma receptors. Tam has suggested that the sedative effect of EKC can mask the observable sigma type behavioral responses. Our purpose in the present study was to investigate whether EKC can affect the PCP-induced stereotyped behaviors in rats. Male Wistar rats (200–300 g) were used. Stereotyped behaviors induced by PCP and SKF 10,047, dopamine-dependent behaviors induced by methamphetamine and apomorphine and serotonin-dependent behaviors induced by *p*-chloroamphetamine and 5-methoxy-N,N-di-methyltryptamine (5-MeODMT) were recorded by the method of Nabeshima *et al.*, Watanabe *et al. and Lee et al.* with some modification, respectively. PCP produced hyperactivity, ataxia and stereotyped behaviors consisting of sniffing, turning, head-weaving and backpedalling. PCP (7.5 mg/kg)-induced stereotyped behaviors were dose-dependently antagonized by EKC (0.25–4 mg/kg). Mr 2266 (2.5 mg/kg), a selective kappa opiate antagonist, antagonized the effect of EKC on PCP-induced stereotyped behaviors. Mr 2266 failed to affect PCP-induced stereotyped behaviors. It is known that PCP-induced stereotyped behaviors are mediated by the dopaminergic and serotonergic neuronal systems. Therefore, we investigated whether EKC affects the dopaminergic and/or serotonergic neuronal systems. EKC antagonized methamphetamine (a dopamine releaser)-induced dopamine-dependent behaviors and *p*-chloroamphetamine (a serotonin releaser)-induced stereotypy, but not apomorphine (a dopamine receptor agonist)-induced dopamine-dependent behaviors and 5-MeODMT (a serotonin receptor agonist)-induced serotonin-dependent behaviors (hind-limb abduction, forepaw treading and Straub tail reaction). These results suggest that EKC, a presumed kappa opioid receptor agonist, antagonized the PCP-induced stereotypy

by an interaction with kappa receptors, and that EKC may reduce dopamine and serotonin release, as a result PCP induced stereotypy is antagonized. Tam, S. W. *Proc Natl Acad Sci USA* **80:** 6703–6707, 1983. Nabeshima, T. *et al. Eur J Pharmacol* **91:** 455–462, 1983. Watanabe, H. *et al. Pharmacol Biochem Behav* **14:** 494–496, 1981. Lee, A. J. *et al. Neuropharmacology* **18:** 153–158, 1978.

[^{3}H]PCP-3-OH AND [^{3}H] (+)SKF 10047 BIND TO MULTIPLE SIGMA/OPIATE PCP BINDING SITES IN RAT BRAIN. Itzhak, Y. Department of Pharmacology, Hadassah School of Medicine, Jerusalem, Israel.

Previous studies have indicated that specific binding of [^{3}H]PCP and [^{3}H] (+)SKF 10047 in rat brain membranes is associated with a common binding site for both PCP analogs and psychotomimetic opiate benzomorphans. This site was designated as *sigma* opiate/PCP receptor. It has also been reported that the antipsychotic agent, haloperidol, is a potent inhibitor of [^{3}H] (+)SKF 10047 specific binding in mammalian brain membranes. In the present study we have characterized the binding properties of one of the most potent analogs of PCP: [^{3}H]PCP-3-OH, and compared it to the binding of [^{3}H] (+)SKF 10047 in rat brain membranes. Both competition and saturation binding assays revealed that [^{3}H]PCP-3-OH labels two distinct binding sites. High affinity (kd < 1 nM) sites are potently inhibited by both psychotomimetic opiates, such as (+)SKF 10047, and PCP analogs and display pharmacological specificity similar to that for [^{3}H] (+)SKF 10047 binding sites. However, low affinity (kd=20 nM) sites are sensitive only to PCP analogs. These two sites are insensitive to haloperidol. [^{3}H] (+)SKF 10047 labels apparently not only a site which displays pharmacological specificity similar to that for high affinity [^{3}H]PCP-3-OH binding site, but also an additional site which is sensitive to haloperidol. Several lines of evidence suggest that this haloperidol sensitive site may be allosterically coupled to the high and low affinity sites labeled with [^{3}H]PCP-3-OH. The present study provides evidence for the existence of multiple subtypes of binding sites for psychotomimetic agents.

PHARMACOLOGY AND NEUROPROTECTIVE EFFECTS OF THE NMDA ANTAGONIST MK-801. Iversen, L. L., G. N. Woodruff, J. A. Kemp, A. Foster, R. Gill and E. Wong. Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR, England.

MK-801, (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine maleate, was described previously as a potent orally active anticonvulsant of unknown mechanism (Clineschmidt *et al.*, 1982). We found that ^{3}H-MK-801 binds to a specific population of receptor sites in rat brain, and these appear to be associated with glutamate receptors of the N-methyl-D-aspartate (NMDA) type (Wong *et al.*, 1986). Thus MK-801 antagonises the depolarising actions of NMDA in rat cerebral cortex *in vitro* and leaves responses to other selective glutamate-like agonists unchanged (quisqualic acid, kainic acid). The antagonism is non-competitive and agonist-dependent in character. We have studied the protective effect of MK-801 against neuronal degeneration caused by ischaemia in the gerbil and by injection of NMDA or quinolinic acid in the rat brain. MK-801 given 1 hr prior to bilateral carotid artery occlusion (5 min in the gerbil) significantly protected against ischaemia-induced loss of CA1 and CA2 hippocampal cells, with an ED_{50} of 0.3 mg/kg (IP), similar to its anti-convulsant potency. MK-801 remained surprisingly effective even when given after the ischaemic episode, with full neuroprotection at 2 hr, and partial efficacy with a 24 hr delay. Pretreatment of rats with 1–10 mg/kg MK-801 IP 1 hr prior to injection caused almost complete protection of neuronal degeneration caused by NMDA (hippocampus and striatum), or quinolinic acid (striatum) ($p<0.05$). MK-801 was also able to yield significant neuroprotection when administered 1–3 hr after neurotoxin injections. MK-801 also showed neuroprotective effects in other ischaemic models (rat 4-vessel, cat-middle cerebral artery). The results provide strong support for the hypothesis that NMDA receptors are involved in ischaemic neurodegeneration and suggest a therapeutic potential for MK-801 in the treatment of cerebral ischaemia. Clineschmidt, B. V., G. E. Martin and P. R. Bunting. *Drug Dev Res* **2:** 123–134, 1982. Wong, E., J. A. Kemp, T. Priestley, A. R. Knight, G. N. Woodruff and L. L. Iversen. *Proc Natl Acad Sci USA* **83:** 7104–7108, 1986.

PSYCHOPHARMACOLOGICAL PROFILE OF THE NMDA RECEPTOR ANTAGONIST MK-801. Iversen, S. D., L. Singh, R. J. Oles and M. D. Tricklebank. Merck Sharp & Dohme Research Centre, Harlow, U.K.

The non-competitive NMDA receptor antagonist, MK-801 induces a complex behavioural syndrome in the rat involving lateral head weaving, body rolling, hyperlocomotion and ataxia. Similar behaviours are seen after the ICV administration of 2-DL-amino-7-phosphonoheptanoic acid (APH), a competitive NMDA receptor antagonist, or following systemic injection of phencyclidine (PCP), ketamine and (+)-SKF 10,047, compounds having high affinity for *sigma* recognition sites, in addition to an antagonist action at NMDA receptors. In drug discrimination studies, PCP, ketamine and SKF 10,047 generalised to the introceptive cue induced by MK-801 while MK-801, ketamine, (+)-SKF 10,047 and APH (given ICV) generalised to that induced by PCP. These findings are inconsistent with the involvement of the *sigma* recognition site in the expression of the motor and discriminative stimulus properties of MK-801, since both MK-801 and APH possess negligible affinity for this site. The ability of MK-801, APH, ketamine, PCP and (+)-SKF 10,047 to block the neurophysiological actions of N-methyl-D-aspartate suggests that their overt behavioural effects are mechanisms based in the NMDA receptor, although various neurotransmitters may be involved in the full expression of these behaviors.

COMPOUNDS BASED ON 2-MDP AND DEXOXADROL WITH POTENTIAL PCP-LIKE PHARMACOLOGICAL ACTIVITY: SYNTHESIS AND RECEPTOR BINDING. Jacobson, A. E., A. Thurkauf, M. V. Mattson, K. C. Rice and J. H. Woods.* National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892; and *Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109.

(−)-2-Methyl-3,3-diphenyl-3-propanolamine (2-MDP) has