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