and human brain membranes. At a low ionic strength the studies of the binding of both $^3$H-PCP and $^3$H-TCP over a wide range of concentrations (0.1 nM to 3 $\mu$M) show the existence of two binding sites on rat brain membranes. Both $^3$H-TCP (Kd=4.8 nM) and $^3$H-PCP (Kd=11.9 nM) bind to the same extent (Bmax=0.93 to 1.04 pmol/mg protein) to high affinity sites. The number of low affinity sites for $^3$H-PCP (Kd=610 nM, Bmax=5.6 pmol/mg protein) is double that for $^3$H-PCP (Kd=320 nM, Bmax=2.8 pmol/mg protein). Competition experiments show that both ligands interact with interdependent high affinity sites through the same molecular component. Biochemical and autoradiographic methods have been used to localize the binding sites of $^3$H-TCP in the rat brain. We have shown that high affinity sites for $^3$H-TCP are present only in the forebrain, mainly in the hippocampus and the cortex. In the hindbrain there are low affinity binding sites which seem different from that characterized in the forebrain. These sites (Kd=50 to 80 nM) are most abundant in the cerebellum (Bmax=1 pmol/mg protein). High and low affinity binding sites for $^3$H-TCP are also present in the human brain. In the frontal cortex the two sites are characterized by the following parameters: Kd=2 nM, Bmax=0.1 pmol/mg and Kd=66 nM, Bax=1 pmol/kg for high and low affinity, respectively. No changes were observed in this region in parkinsonian brain. The temporal cortex is rich in high affinity sites while in the cerebellum a very large number of lower affinity sites was evidenced (Kd=277 nM and Bmax=5.5 pmol/mg protein). These multiple binding sites will be discussed according to their putative functions.

N-ALLYLNORMETAZOCINE (SKF 10,047) BLOCKS NMDA NEUROTOXICITY AND HYPOXIC NEURONAL INJURY IN CORTICAL CULTURES. Choi, D. W., M. P. Goldberg and V. Viseskul. Department of Neurology, Stanford University School of Medicine, Stanford, CA 94305.

The prototypical "sigma" receptor ligand, N-allylnormetazocine (SKF 10,047) has been reported to antagonize the neuroexcitatory effect of N-methyl-D-aspartate (NMDA) on spinal neurons. Recently, Olney and colleagues (*Neurosci Lett* **68**: 29–34, 1986) reported that SKF 10,047 could antagonize the acute "excitotoxic" degeneration produced by NMDA on chick embryo retinal neurons. This study was performed to see if SKF 10,047 had similar protective efficacy on mammalian cortical neurons. A five min exposure of murine cortical cell cultures to 500 $\mu$M NMDA resulted by the following day in widespread neuronal disintegration, accompanied by substantial efflux of lactate dehydrogenase to the bathing medium. Widespread neuronal loss was also produced without addition of exogenous toxin, by exposing the cultures to hypoxia for 8 hours. Addition of 100 $\mu$M (+)-SKF 10,047 to the exposure solution markedly attenuated both types of neuronal cell loss: surviving neurons remained morphologically stable, excluded trypan blue dye, and released little lactate dehydrogenase to the culture medium. These observations are consistent with the notion that sigma receptor ligands may offer clinical therapeutic utility in hypoxic encephalopathy, or other disease states characterized by NMDA receptor-mediated neuronal damage. (Supported by NIH grant NS12151.)

KETAMINE AND MK801 AS NEUROPROTECTIVE AGENTS IN CEREBRAL ISCHEMIA/HYPOXIA. Church, J., S. Zeman and D. Lodge. Department of Physiology, Royal Veterinary College, London NW1 0TU, U.K.

Recent evidence suggests that the vulnerability of certain neuronal populations to ischemia/hypoxia is a consequence of a direct toxic effect of an accumulation of synaptically-released excitatory amino acids acting at post-synaptic receptors (in particular, the N-methylaspartate (NMA) receptor subtype) located on the vulnerable neurons. However, whereas *in vitro* both competitive and non-competitive NMA antagonists effectively prevent anoxic death of these vulnerable neurons, the results obtained from *in vivo* experiments are less consistent. Using a long-term recovery model of cerebral ischemia in the rat which results in a reproducible degree of neuronal damage in the selectively vulnerable hippocampal CA1 region, we have studied the possible therapeutic efficacy—judged histologically after a 7 day recovery period—of the systemically active NMA antagonists ketamine and MK801. Doses of both drugs, and their frequency of administration, were chosen on the basis of the known degree and time course of NMA antagonism seen *in vivo* following their systemic administration. Ketamine, administered IV and IP in various doses either prior to and/or following a 10 min ischemic insult, failed to lessen hippocampal CA1 neuronal damage, even when administered in divided doses (up to a total of 60 mg/kg) which might have been expected to result in substantial NMA antagonism both during the period of ischemia itself and for at least 8 hr after it. A cumulative dose of 210 mg/kg ketamine did however provide significant ($p<0.05$) protection after 10 min ischemia, although following a 6 min ischemic insult (which resulted in less CA1 neuronal loss than was seen after 10 min ischemia) the same dose of ketamine worsened outcome. In contrast, MK801 0.25 or 0.5 mg/kg IV administered immediately before 10 min ischemia resulted in significant ($p<0.05$ and $p<0.001$ respectively) protection: at the 0.5 mg/kg dose, 66% of CA1 pyramids were judged histologically normal compared with 7% in non-treated control animals. Initial studies suggest, however, that such a level of protection may not be achieveable in this model should administration of the drug be delayed until after the ischemia. These results suggest that NMA receptor-mediated excitation may contribute to the neuronal damage in selectively vulnerable regions following ischemia but also emphasize that the possession by a PCP-like compound of NMA antagonist properties may not alone determine its neuroprotective activity *in vivo*. This will be influenced by the effects of the compound on a variety of other neurotransmitter and regulatory systems (e.g., control of intracranial pressure), which may combine to worsen the neurological outcome despite adequate NMA receptor blockade. (Supported by the Medical Research Council and Wellcome Trust.)

BIOCHEMICAL AND BEHAVIORAL CHARACTERIZATION OF PCP AND SIGMA OPIOID RECEPTORS. Contreras, P. C., R. P. Compton, J. B. Monahan and T. L. O'Donohue. Searle Research and Development, G. D. Searle & Co., St. Louis, MO 63198.

Phencyclidine (PCP) is one of the most abused drugs in