recently been shown by Tang *et al.* (1984) to have PCP-like pharmacological activity. We have found that its affinity for the PCP receptor (as defined by [^{3}]TCP) is about the same as PCP itself. We found it intriguing that the open-chain compound could mimic, in its receptor affinity and pharmacological activity, PCP's actions. Based on our determination of the conformation of dexoxadrol which overlaps pertinent moieties in PCP (from our study of the absolute configuration of dexoxadrol [Jacobson *et al.*, 1987]), the presumed significant atoms of 2-MDP will overlap more readily with those of PCP and dexoxadrol if the molecule is modified. Thus, we synthesized a number of analogs of 2-MDP (4-hydroxy-2-methyl-4-phenylbutylamine, 4,4-diphenyl-4-hydroxy-2-methylbutylamine, 4,4-diphenyl-4-hydroxybutylamine, 4,4-diphenyl-4-hydroxy-2,N-dimethylbutylamine, 3,3-diphenyl-3-hydroxypropylamine, and 4,4-diphenyl-4-hydroxy-3-methylbutylamine. The receptor binding affinities of these compounds have been determined, and their discriminative stimulus properties are being examined. It was noted by Hardie *et al.* (1966), that N-derivatives of dexoxadrol retained some of the biological activities of dexoxadrol itself. Insofar as we were aware, these compounds had never been examined for their affinity for the PCP receptor. In order to find the biochemical effect of the molecular change from a secondary to a tertiary or quaternary nitrogen atom in dexoxadrol, we prepared the N-methyl, N-benzyl, and N-allyl dexoxadrol, as well as the N-dimethyl quaternary salt of dexoxadrol, and determined their affinity for the PCP receptor. These results, as well as those with the 2-MDP analogs, will be discussed. (A.T. supported by the National Institute on Drug Abuse through National Research Service Award No. 5F32 DAO5287-02.)

N-METHYL-D-ASPARTATE ENHANCED ^{3}H-TCP BINDING TO RAT CORTICAL MEMBRANES: EFFECTS OF DIVALENT CATIONS AND GLYCINE.

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PCP and related substances can potently and specifically antagonize excitatory amino acid depolarizations mediated by the N-methyl-D-aspartate (NMDA) receptor. Pharmacological evidence strongly suggests that the inhibition of NMDA-induced excitation by PCP is not competitive in nature and that PCP and related drugs act instead to block the open state of the NMDA-activated ion channel. In accord with this model is the report by Fagg and Baud (1986) that the binding of ^{3}H-TCP to membrane preparations rich in postsynaptic densities can be greatly enhanced by addition of exogenous L-glutamate (Glu) and that this effect is mediated by action on the NMDA receptor. We report here our own investigations of excitatory amino acid induced ^{3}H-TCP binding in rat cortical homogenates that have been lysed twice in distilled H_2O (30 min at 37°C) and washed repeatedly in 10 mM HEPES (pH 7.5). This final membrane preparation is referred to as the twice lysed P_2 (LLP). Initial studies revealed that in the crude P_2, specifically-bound TCP was 90% of total binding (2.5 nM ^{3}H-TCP, non-specific binding measured in the presence of 300 μM PCP) which was reduced up to 80% in the LLP. The addition of NMDA increased TCP binding two- to three-fold (K_d=2.5 μM), although the maximal enhancement (at 100 μM NMDA) was still below that seen in the P_2. Agonists at the other excitatory amino acid receptors, kainate or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), were without effect. Glu and aspartate (both at 1 μM) produced a three-fold increase in ^{3}H-TCP binding. Our most recent experiments have established that low concentrations of both $MgCl_2$ and $CaCl_2$ can enhance TCP binding in the LLP although both these cations could inhibit binding at 1 mM. The enhancement of binding by these ions may reflect the presence of low concentrations of endogenous ligand for the NMDA receptor as these effects were blocked by DL-2-amino-5-phosphonovalerate (APV). We have also found that glycine (0.1 and 1 μM) can enhance TCP binding via a mechanism that is reversible by APV but not by strychnine. These studies suggest that divalent cations and glycine enhance binding by stabilizing the NMDA channel in the open state. (Supported by DA-02073.)

REORGANIZING GLUTAMATE PATHWAYS IN THE DEVELOPING BRAIN MAY PROVIDE A SUBSTRATE FOR HYPOXIC-ISCHEMIC NEURONAL INJURY.

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Hypoxia-ischemia damages selected regions of the fetal and neonatal brain. The basal ganglia and hippocampus are especially vulnerable and significant injury is usually accompanied by damage to the hippocampus manifested by seizures. We studied the distribution of glutamate receptors in human fetal and infant brain using *in vitro* receptor autoradiography. The globus pallidus (GP), which lacks a glutamate innervation in the adult brain, is heavily endowed with glutamate receptors in the newborn. Studies in rats suggest that the caudate-putamen and the GP at 7 days of age both contain adult densities of glutamate receptors which disappear over the next 2 weeks in the GP. Autoradiography of fetal human brain shows heavy concentrations of glutamate receptors in the caudate, GP, sub-thalamic nucleus and the reticular nucleus of the thalamus by 18–24 weeks gestation. In a model of unilateral hypoxic-ischemic injury in 7 day old rats, glutamate receptors in the caudate and GP and hippocampus are markedly reduced and histologic injury correlates well with the distribution of receptors in the vulnerable structures. Pharmacologic characteristics of the glutamate receptors in the immature brain appear to be unique and dissimilar from those in adulthood. Microinjection of the glutamate analogue quisqualic acid destroys glutamate receptor bearing areas in the immature rat and replicates key features of hypoxic-ischemic brain injury. The characteristics of the immature glutamate receptors, their co-localization with TCP receptors and the neuroprotective effects of glutamate blocking compounds are subject of cur-