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-

rent study. Transient expression of glutamate receptors in the developing brain may provide an explanation for patterns of selective vulnerability. Modification of excitatory neurotransmission in the fetus and newborn brain may reduce brain injury (e.g., cerebral palsy).

NEUROCHEMICAL AND BEHAVIORAL EVIDENCE FOR A CENTRAL INDIRECT CATECHOLAMINERGIC AGONIST ACTIVITY OF GK 13. Kamenka,* J. M., J. J. Bonnet, M. Slimani, D. Boucher and J. Costentin. U.A. 1170 C.N.R.S., Université de Rouen, 76800 Saint Etienne du Rouvray, *Ecole Nationale Superieure de Chimie, L.P. 8402 C.N.R.S., 34075 Montpellier, France.

GK 13 is a benzothiophene derivative of phencyclidine. It does not possess the phenylethylamine structure common to various substrates of the neuronal catecholamine uptake complexes. However it seems to behave as an indirect catecholamine agonist. The present studies aim to verify this assertion and to prove its mechanism(s) of action. On a synaptosomal fraction prepared from rat striatum, using a double labelling test which assesses simultaneously the effect of a drug on the ^{3}H-dopamine (DA) influx and the 14C-DA efflux, we observed that GK 13, at a 3.10^{-7} M concentration inhibits completely the ^{3}H-DA uptake, with an IC50 of about 3.10^{-8} M. A ^{14}C-DA release occurs from 10^{-9} M, in a concentration dependent manner. It reaches about 50% of the 14C-radioactivity stored in synaptosomes for a 10^{-6} M concentration. Such a neurochemical profile has some similarities with that of amphetamines. These substrates of the DA uptake complex have a low affinity for the site modulating the DA uptake to which bind pure DA uptake inhibitors such as nomifensine, mazindol, GBR 12783. This point distinguishes GK 13 from amphetamines because it is a potent competitor for the specific binding of 3H-GBR 12783 to this modulatory site (IC50 $\simeq 10^{-8}$ M). In addition, GK 13 is less effective to inhibit 3H-Norepinephrine uptake (synaptosomes from hypothalamus, IC50=0.22±0.02 μM) than ^{3}H-DA uptake. Administered systematically to mice GK 13, from a 4 mg/kg dose, increases in a dose dependent manner their locomotor activity. This effect occurs rapidly (<10 min) and is long lasting (>4 hr). Similarly to dexamphetamine it partially antagonizes reserpine-induced hypothermia but it poorly reverses reserpine-induced akinesia.

THE CONFORMATIONAL ADAPTATION OF THE PHENCYCLIDINE MOLECULAR PATTERN TO THE LIPOPHILICITY OF ITS SURROUNDINGS. Kamenka, J.-M. and R. Chicheportiche. CNRS LP 8402-INSERM U 249, Ecole Nationale Supérieure de Chimie, 8, rue de l'Ecole Normale 34075 Montpellier-Cédex-France.

The phencyclidine (PCP) molecule is known to possess an uncommon profile making its pharmacological classification difficult. This particular behavior is probably a consequence of the action of the PCP molecule on multiple biological systems. In a search for biochemical specificity we have tested closely related PCP compounds for their ability to interact with ^{3}H-PCP, ^{3}H-QNB, ^{3}H-DHM sites or ^{3}H-dopamine transport, and found some structures to possess interesting specificity. Surprisingly they do not differ very much from phencyclidine. The most striking case is TCP differing only by the aromatic group (a 2-thienyl instead of a phenyl) from the PCP. The difference in terms of lipophilicity or size does not appear important enough to totally explain the increase in specificity. In order to compare these two structures we have made measurements of their conformational equilibria in solution in different classes of anhydrous organic solvents by means of ^{13}C-NMR using the so-called Eliel's method. We found the conformational free-energy of TCP and PCP to be linearly related to the maximum solubility of water in the solvents. The most interesting case was that of oxygenated polar solvents where the conformational equilibria were shifted toward the biologically inactive conformation when the maximum water solubility was reduced. Conversely the biologically active conformation was generated when the maximum water solubility was increased. Such a behavior is interestingly different for PCP and TCP as shown by the different slopes of the linear relationships. It can be concluded: (1) The general pattern of PCP-like molecules seem to behave as "chameleon-like" structures adapting their conformational equilibrium to the lipophilicity of the surroundings, (2) The conformational adaptation seems to be dependent of the geminal aromatic and amino groups, (3) For TCP and PCP the proportion of the biologically active conformation is different in a given medium especially in lipophilic ones. The hypothetical involvement of such a physical comportment in binding and localization characteristics of PCP and TCP will be discussed.

PCP BINDING AND ITS EFFECT ON IMMUNOCYTES *IN VITRO*. Khansari, N. and H. D. Whitten. Department of Veterinary Science, North Dakota State University, Fargo, ND, and Southern State University, Baton Rouge, LA.

Antigenic similarity is being found increasingly among cells of the central nervous system and immune system; e.g., morphine, metenkephalin, *beta*-endorphin, substance P. We have found that radiolabeled PCP can bind to human peripheral blood immunocyte. Binding PCP to various immunocyte subpopulations varied significantly. However, the nature of binding (reversibility and saturability) and the extent of binding were similar to that observed with a *sigma*-receptor positive mouse neuroblastoma-chinese hamster brain hybrid cell line (NCB-20). We found that PCP has suppressive effect on several immunocyte functions (*in vitro*) such as: DNA synthesis, 2-deoxyglucose uptake (monocytes activation), interleukin-1 production and immunoglobulin synthesis. These studies indicate that both humoral and cell-mediated immunity are significantly affected by PCP. More importantly, these results suggest formulation of an hypothesis in which a peripheral anti-receptor immune response (autoimmunity) might enhance that precipitation of a psychosis in part dependent on PCP-*sigma* opioid receptor interaction in the CNS. (Supported in part by Harry Frank Guggenheim Foundation.)