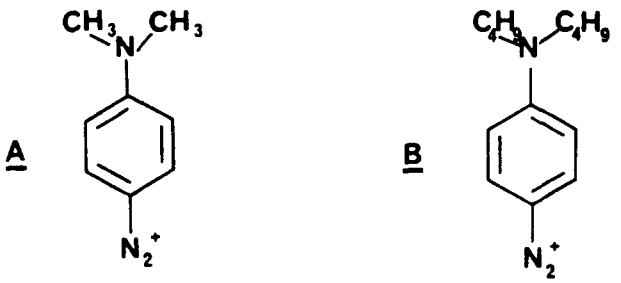
process. As such several p.dialkylamino benzene diazonium salts have been synthesized and tested for their reversible binding characteristics on both the α-bungarotoxin and PCP binding sites of the nicotinic acetylcholine receptor from *Torpedo marmorata*. Among these derivatives two have been studied more thoroughly for irreversible inactivation of the PCP binding site (see below).



Reversible binding: Ki (PCP)

A: 1.7×10^{-4} M	desensitized state	B: 1.6×10^{-6} M
2.5×10^{-4} M	resting state	4×10^{-6} M

Irreversible loss of PCP binding capacity (h.).

A: 40% at 2×10^{-4} M	(either state)	B: 65% at 3×10^{-6} M (desens. state)

Tritiated samples.

A and B: all *four subunits* are labelled
protection by excess PCP 50% for A 90% for B

A heterocyclic derivative: 2-diazoimidazole showed a unique feature. For this chemical, which has a low binding affinity for the PCP binding site (over 10^{-3} M) the photoinducted irreversible blocking is only effective when the receptor is in a desensitized state.

INTERACTIONS BETWEEN THE NMDA-TYPE RECEPTOR COMPLEX AND PCP RECOGNITION SITES. Lehmann, J. and P. L. Wood. Neuroscience/Cardiovascular Research, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, NJ 07901.

While there are a number of different sites of action of phencyclidine (PCP), one common site of action of PCP and a number of its analogs seems to have emerged. This PCP recognition site may be defined by the rank-order of potency of compounds at binding sites labeled by [3H]PCP, [3H]TCP, or [3H]MK-801. The same rank order of potency of PCP analogs is found in the inhibition of NMDA-type receptor-mediated responses: NMDA-elicited increases in firing of neurons measured extracellularly or their depolarization measured intracellularly, NMDA-elicited [3H]ACh release, and, in vivo, cerebellar cGMP levels. The mechanism by which PCP and its analogs inhibit the function of the NMDA-type receptor/effector complex is not known. Several observations indicate that PCP analogs are not competitive antagonists of NMDA-type receptors, for example: (1) Lack of activity of PCP analogs at binding sites labeled by the competitive NMDA-type receptor antagonist, [3H]CPP; (2) Non-competitive kinetics with respect to inhibition of NMDA-induced [3H]ACh release; and (3) Hill coefficients less than one in decreasing cerebellar cGMP (in contrast to competitive NMDA antagonists, which have Hill coefficients of one). Several different models have been proposed to describe the interaction between PCP recognition sites and NMDA-type receptors: (1) A strict analogy to the GABA receptor/benzodiazepine/chloride channel complex, in which the PCP site mediates allosteric regulation of the affinity of glutamate for its receptor; (2) A direct modulation by the PCP recognition site of the ion channel associated with NMDA-type receptors, but which is apparent only when the NMDA-type receptor is occupied by agonist, and opens the ion channel; (3) A binding site for PCP and its analogs within the NMDA-activated ion channel itself, where they block cation flow by steric hindrance. The currently available biochemical and electrophysiological data cannot conclusively reject or prove any of these three models.

STEREOSELECTIVE METABOLISM OF NORKETAMINE, THE *N*-DEMETHYLATED METABOLITE OF KETAMINE, IN RAT LIVER MICROSOMES. Leung, L. Y. and T. A. Baillie. Department of Medicinal Chemistry, University of Washington, Seattle, WA 98195.

The metabolism of the dissociative anesthetic agent, ketamine, ((±)-2-o-chlorophenyl-2-methylaminocyclohexanone) has been studied by a number of groups both *in vitro* and *in vivo*. However, the origin of the isomeric 4-, 5- and 6-hydroxynorketamine metabolites remains unclear. These products could arise from norketamine, the *N*-demethylated metabolite of ketamine, or alternatively, they could be formed from the corresponding hydroxylated metabolites of ketamine. Thus, the intermediacy of norketamine as the precursor to these hydroxylated norketamine derivatives was investigated *in vitro* using both racemic norketamine and the individual enantiomers as substrates for incubations. Norketamine was found to yield the corresponding hydroxylated metabolites in rat liver microsomal preparations. Incubations using the separate enantiomers revealed a pronounced substrate enantioselectivity and product regioselectivity in the formation of these hydroxylated products. Thus, S-norketamine was hydroxylated at the C-6 position to yield exclusively 6-OH norketamine, whereas 4-OH norketamine was produced almost solely from the R-enantiomer. Experiments using pseudoracemic mixtures of norketamine as substrates suggest the presence of enantiomeric interaction on the formation of these hydroxylated products. A previous study on the metabolism of the enantiomers of ketamine itself showed analogous stereoselectivity in the formation of these hydroxylated norketamine metabolites. Our findings thus indicate that norketamine is the intermediate in the metabolic transformation of ketamine to hydroxynorketamine isomers in liver tissues, and lend support to the view that the formation of active metabolites via stereoselective processes may contribute in part to the observed CNS effects of ketamine. (Support by NIH Grant NS 17956.)