larly useful in the further purification of the endogenous ligand of the PCP receptor. Such a ligand may serve as the endogenous modulator of NMDA-receptor mediated mechanisms in the limbic system.

NON-COMPETITIVE REGULATION OF PHENCYCLIDINE/σ RECEPTORS BY THE N-METHYL-D-ASPARTATE RECEPTOR ANTAGONIST D(−)2-AMINO-5-PHOSPHONOVALERIC ACID.

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Electrophysiological and neurochemical studies have established a noncompetitive inhibition of N-methyl D-aspartate-type excitatory amino acid (EAA) receptor mediated CNS phenomena by PCP-like drugs. Anatomical studies have demonstrated similar distribution patterns for limbic PCP/σ receptors and NMDA receptors. These findings suggest a model in which the NMDA and PCP/σ receptors may be separate protein entities within a supramolecular complex. In order to determine the biochemical basis of the interaction between NMDA and PCP/σ receptors, specific binding of [^{3}H]TCP ([2-thienyl]-cyclohexylpiperidine) was determined in the presence of varying concentrations of EAA agonists and of the specific direct NMDA antagonist D(−)2-amino-5-phosphono-valeric acid (D(−)AP5). D(−)AP5 dose-dependently decreased the apparent B_{max} of [^{3}H]TCP binding without affecting apparent K_D. In D(−)AP5-treated membranes, pre-incubation with glutamate at doses of up to 250 μM partially reversed the D(−)AP5-induced decrement in apparent B_{max} of [^{3}H]TCP binding without affecting apparent K_D. D(−)AP5 maximally inhibited [^{3}H]TCP binding >95%. A Hill coefficient of -1.04 ± 0.23 calculated from this binding data suggested that D(−)AP5 mediates its inhibitory effects on [^{3}H]TCP binding via interaction at a single (NMDA) receptor. The IC_{50} of D(−)AP5 for inhibiting [^{3}H]TCP binding is comparable to its IC_{50} in electrophysiological paradigms. Following osmotic lysis, freezing for 48 hr and thawing of the crude membrane pellet the IC_{50} of inhibition of [^{3}H]TCP binding by D(−)AP5 decreased significantly. The rank order of a series of amino acid receptor antagonists for displacement of 10 nM [^{3}H]TCP were D(−)AP5 > D-α-aminoadipate > 1-glutamyl diethylester, corresponding to their known rank order of potency as direct NMDA receptor antagonists. These data support the hypothesis that D(−)AP5 exerts its effects on [^{3}H]TCP binding via a specific interaction with NMDA receptors. This study provides the first evidence from a receptor-binding paradigm for a non-competitive interaction between PCP/σ and NMDA receptors. The ability of D(−)AP5, a selective NMDA receptor antagonist, to abolish [^{3}H]TCP binding is consistent with the hypothesis that PCP/σ receptors may be solely localized to an NMDA receptor complex. The ability of [^{3}H]TCP to bind to an activated NMDA receptor complex suggests that TCP might be a useful probe of NMDA receptor functioning *in vitro*. The PCP receptor-endogenous ligand-NMDA receptor-ion channel complex appears to constitute an important functional CNS unit.