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# Phencyclidine Receptors and N-Methyl-D-Aspartate Antagonsim: Electrophysiologic Data Correlates With Known Behaviours

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MARTIN, D. AND D. LODGE. *Phencyclidine receptors and N-methyl-D-aspartate antagonism: Electrophysiologic data correlates with known behaviours.* PHARMACOL BIOCHEM BEHAV 31(2) 279–286, 1988.—Using cortical wedges and isolated frog spinal cords, the potency of a series of psychoactive phencyclidine (PCP) and sigma receptor ligands as antagonists of N-methyl-D-aspartate (NMDA) has been compared with their potency in neurochemical and behavioural studies. Phencyclidine receptor, but not sigma or kappa, ligands were selective antagonists of NMDA on both preparations. Combination studies suggested that dissociative anaesthetics and sigma benzomorphans act at the same site. The relative potencies of the drugs as NMDA antagonists correlated well with their potency in PCP receptor binding studies in vitro and in PCP discrimination studies in vivo.

Excitatory amino acids N-Methyl-D-aspartate Phencyclidine Sigma opiates Receptors Discrimination studies

DISSOCIATIVE anaesthetics of the arylcyclohexylamine class, e.g., ketamine and PCP, and the dioxalane class, dexoxadrol and etoxadrol, have several behavioural, neurophysiological and biochemical features in common with sigma opiates of the benzomorphan type, e.g., cyclazocine and SKF 10,047. In man, several of these compounds have abuse potential and produce similar subjective effects (9,21). Discrimination studies in animals demonstrate cross generalisation between these drugs (3, 4, 17, 18, 43, 44), and in the chronic spinal dog preparation both types of drug induce similar neurophysiological changes as well as the syndrome of canine delirium (37,51).

The neuronal substrate for these effects may be the PCP binding site present on rat brain membranes which has a $K_d$ of about 200 nM (52,58). Binding of [$^3$H]-PCP can only be displaced by dissociative anaesthetics and sigma opiates and not by other opiates and hallucinogens (15, 41, 57, 59). Affinities and relative potencies of drugs at this binding site correlate well with potencies in behavioural studies, a finding which suggests a physiological relevance for this PCP receptor.

Other studies, however, showed that sigma opiates bound to a naloxone-insensitive site with a pharmacological profile quite different to that above (10, 19, 35, 49, 50, 55). This paradox has now been largely settled by resolving (+) SKF 10,047 binding into high and low affinity sites. Haloperidol, (+) 3-PPP, U50,488H and (+) pentazocine potently displace binding at the former site but it is the latter, low affinity, site at which PCP and other dissociative anaesthetics appear to act (10, 28, 45). These receptors have been named the sigma and PCP receptors respectively (40). Discussion continues as to the behavioural effects subserved by each (48).

Despite considerable interest over several years, there has been no real concensus on how PCP and sigma ligands modulate neuronal activity, dopaminergic, cholinergic, purinergic, calcium, potassium and sodium channel mechanisms having all been proposed (8,22).

Following the description of a selective reduction by PCP of the excitatory effects of N-methyl-D-aspartate (NMDA) on mammalian CNS neurones (29), dioxalanes, benzomorphans, morphinans, etc. have since been shown to antagonise NMDA in vivo (1, 2, 5, 31). NMDA is a selective agonist for subtype of excitatory receptor at which glutamate is thought to mediate synaptic transmission in the mammalian brain (13, 34, 53). Because the technique of microelectrophoresis has some limitations for quantification (11), in vitro techniques have been employed to explore the relationship between PCP receptor activation and NMDA antagonism. To date, however, only indirect assessment of depolarisation (32,46) or small numbers of drugs (16, 27, 36) have been employed.

To test the correlation of NMDA antagonist potency with both PCP binding and behavioural studies, we have now examined a range of ligands for the PCP and sigma receptors on two in vitro preparations of vertebrate CNS, i.e., rat cerebral cortical slices (16) and frog hemisected spinal cords (6).

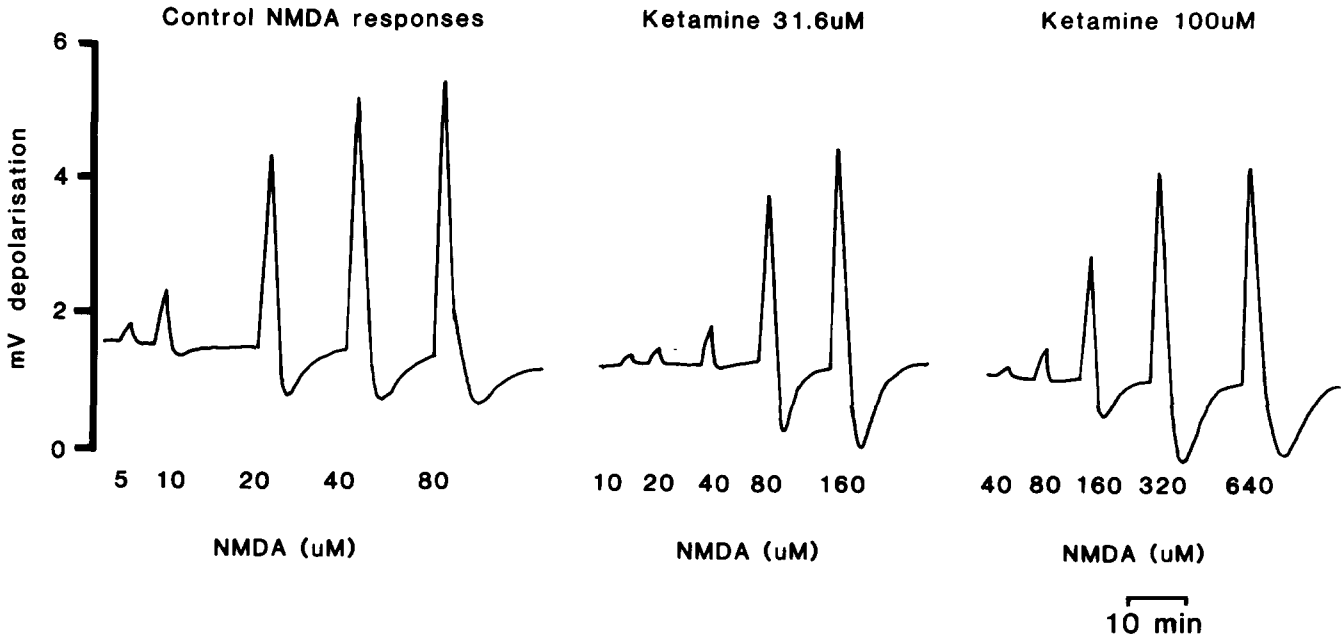


FIG. 1. Effect of ketamine on depolarisations induced by NMDA in a rat cortical wedge preparation. The traces show the dose response relationship of NMDA. Ketamine (100 $\mu$M) reduced the maximal effect of NMDA as can be seen by comparing the responses to 320 and 640 $\mu$M NMDA with the control response to NMDA 80 $\mu$M.

## METHOD

Standard methods (16) were used to prepare cortical wedges. Wistar rats (200–400 g) were killed by decapitation and the brain removed and placed into chilled artificial cerebrospinal fluid (aCSF). Transverse slices of forebrain 500 $\mu$m thick were made using a vibroslice (Camden Instruments). Further cuts were made at the midline and just lateral to each cingulum in order to produce wedge-shaped tissue pieces which contained white and grey matter.

Such cortical wedges were placed in a bath divided by a Perspex barrier so that the grey matter was mostly in one compartment but also passed through a silicone grease-filled slot in the lower half of the Perspex barrier so that the white matter was entirely within the second compartment. A second piece of Perspex placed on top of the lower barrier formed a high resistance seal between the two compartments.

Each compartment was perfused independently (2 ml/min) at room temperature (20–23°C) with aCSF of the following composition mM: NaCl 124, $NaHCO_3$ 25.5 KCl 3.3, $KH_2PO_4$ 1.2, $CaCl_2$ 2.5, $MgSO_4$ 1.0 or 0, and glucose 10, equilibrated with 5% $CO_2$ in $O_2$. Slices were initially perfused with magnesium containing medium, but experiments were performed in magnesium-free medium to maximise NMDA-induced depolarisations. Tetrodotoxin (TTX) was added initially at 2.5 $\mu$M to block regenerative sodium potentials and maintained at 0.1 $\mu$M.

The D. C. potential between the two compartments was monitored with Ag/AgCl electrodes via an agar/saline bridge, amplified (Neurolog NL106) and continuously displayed on a chart recorder (Bryans BS234).

The effects of amino acid agonists and antagonists on motoneurons of frog hemisected spinal cord were tested as previously described (36). Briefly, each hemicord was placed in a Perspex chamber perfused at 1 ml/min with 10–12°C magnesium-free frog Ringer containing 10 mM Tris buffer and 0.1 $\mu$M TTX. D. C. Potentials were recorded between a ventral root and the spinal cord across a liquid paraffin/petroleum jelly seal.

After an initial 2 hour stabilisation period the normal perfusion was interrupted by 4 ml (cortex) and 1 ml (cord) aliquots of medium containing agonists at different concentrations in order to prepare dose-response curves.

Having established stable agonist-induced dose-response curves to either NMDA, quisqualate or kainate the tissue was equilibrated with antagonists for 1 hour and the dose-response relationships reassessed; each point on the dose-response curve was the mean of determinations on at least 4 preparations on tissue taken from at least two animals. Since some of the excitatory amino acid antagonists displayed noncompetitive properties, $IC_{50}$ values against 40 $\mu$M NMDA (rather thatn $pA_2$ estimates) were determined.

The following drugs were used in these studies, with sources in parentheses: N-methyl-D-aspartic and kainic acid (Sigma), quisqualic acid (H. Shinozaki), MK-801 maleate (MSD Laboratories), phencyclidine HCl, thienylcylohexylpiperidine HCl, (+) and (−) cyclazocine HCl, (+) and (−) SKF 10,047 (NIDA), (+) and (−) 3-methyl-phenycyclidine HCl (R. G. Browne) and ketamine HCl (Warner-Lambert). Stock solutions were prepared by diluting acids in equal molarities of NaOH and salts in distilled water, pH being adjusted to 7.2–7.6 if necessary.

## RESULTS

During the stabilisation period both cord and cortex frequently displayed spontaneous activity which was abolished by TTX.

Superfusion of the three excitatory amino acid agonists (2.5–160 $\mu$M) produced dose-dependent depolarisations in cortical wedges and hemisected cords. Responses to NMDA and kainate had slow time courses compared to quisqualate.

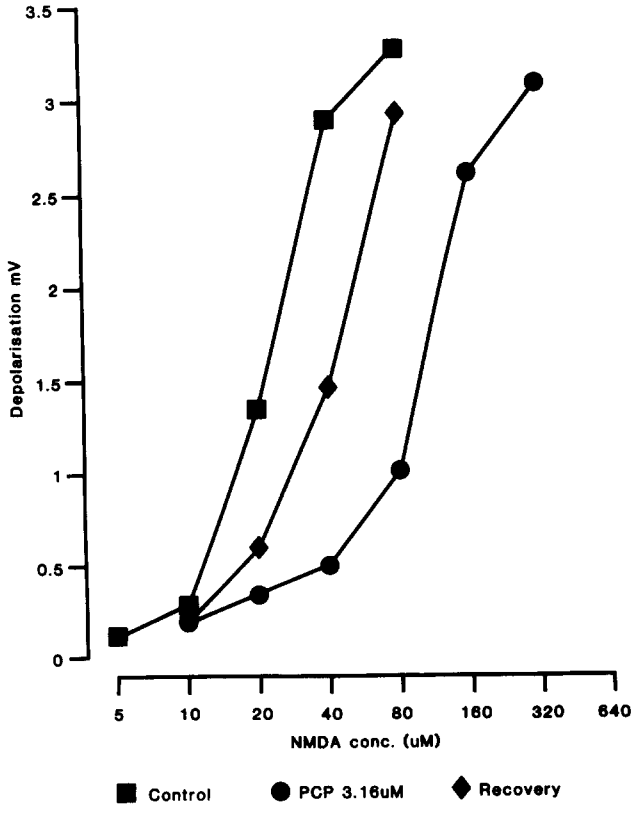


FIG. 2. Effect of phencyclidine on the dose-response curve to NMDA of a rat cortical wedge preparation. The rightward shift of the dose-response curve by 3.16 $\mu$M PCP is partially reversed after 90 min washing in drug-free medium.

It had previously been reported that large concentrations of NMDA and kainate produced depression of subsequent responses and, therefore, concentrations greater than 80 $\mu$M were not used in predrug controls (16,36).

As reported previously on frog spinal cords (36), ketamine reduced the depolarising action of NMDA on rat cortical wedges (Fig. 1). At low concentrations of ketamine (<10 $\mu$M), there was a near parallel shift in the dose-response curves but at 31.6 and particularly at 100 $\mu$M, the curves are flatter and the maximal response to NMDA is reduced, features characteristic of noncompetitive antagonism (Fig. 1). $IC_{50}$ values for ketamine against NMDA 40 $\mu$M were 11.6±2.5 $\mu$M and 8.9±0.8 $\mu$M in the rat cortex and frog cord respectively. These actions of ketamine were reversed after 2 hr of washing in control medium.

In both preparations other dissociative anaesthetics, PCP and thienylcyclohexylpiperidine (TCP) and the benzomorphans, SKF 10,047 and cyclazocine, selectively reduced responses to NMDA. Dose-response curves for NMDA were shifted to the right by these antagonists often in a near parallel fashion (Figs. 2, 3 and 4), although it was unusual to get full recovery from the effects of these four antagonists (Fig. 2). Depolarising responses to quisqualate, kainate and potassium were unaffected by concentrations of PCP receptor ligands that considerably reduced the action of NMDA. For example, 10 $\mu$M (+) cyclazocine had less effect on kainate- and potassium-induced depolarisations than did 3.16 $\mu$M on responses to NMDA (Fig. 3).

The dibenzocycloalkenimine, MK-801, a novel anticonvulsant and potent PCP receptor ligand (56), also attenuated NMDA-induced depolarisations in a dose-dependent manner having no effect on responses to kainate and quisqualate. MK-801 proved to be the most potent NMDA antagonist tested (see Table 1). Its actions were not fully reversible despite several hours of washing and testing with NMDA. The antagonism of NMDA by MK-801 appeared to be use-dependent and examination of this phenomenon is reported elsewhere (7).

Dissociative anaesthetics and sigma opiates display stereoselective effects in both binding and behavioural studies. We examined the optical isomers of the 3-methyl-phencyclidine (PCMP), of SKF 10,047 and of cyclazocine as excitatory amino acid antagonists. The (+) isomer of PCMP was found to be approximately 12–15 times as potent as the (−) isomer as an NMDA antagonist. The higher potency of (+) isomers of dissociative anaesthetics as NMDA antagonists agrees with previous results with this compound (27) and with ketamine (30). With the benzomorphans, however, the stereoselectivity varied between compounds. Thus (+) SKF 10,047 was approximately 3 and 5 times as potent as the (−) isomer for cord and cortex respectively, whereas with cyclazocine (−) isomer was approximately 3 and 4 times as potent as the (+) isomer respectively. This stereoselectivity as NMDA antagonists is not dissimilar to that found previously in vivo (2,31).

A good correlation existed between the $IC_{50}$ values for NMDA antagonists in the two preparations. Using a least squares method, the slope of the regression line was 0.97 ($p<0.05$). The apparent anomaly, that MK-801 was relatively weak on the frog spinal cord, may have been due to the lower temperature of the frog preparation since the rate at which MK-801 blocks NMDA responses is temperature-dependent (7).

The rank order of potency of these compounds as NMDA antagonists in vitro also correlated well with that in vivo on mammalian spinal neurones [(31); and see Table 2]. The Spearman rank correlation statistic (r) for in vitro and in vivo data was >.9 ($p<0.01$). Such good correlations with a range of dissociative anaesthetics and sigma opiates suggest that the pharmacological characteristics of the NMDA receptor-ionophore complex are very similar in all three preparations.

Other more specific sigma (rather than PCP receptor) ligands had no selective effect on NMDA responses. Thus, on frog motoneurones, the high affinity sigma ligand haloperidol (1–100 $\mu$M), had no effect on the dose-response curves to NMDA, quisqualate and kainate. Similarly mu receptor ligands, e.g., morphine (100 $\mu$M), naloxone (10 $\mu$M), and kappa agonists, e.g., U50,488H (1–100 $\mu$M), tifluadom (0.1–10 $\mu$M), were also without selective effects on amino acid responses.

To determine whether sigma opiates and dissociative anaesthetics share a common site to produce NMDA antagonism, combination studies were conducted on rat cortical wedges. Individually ketamine (31.6 $\mu$M) and (+) SKF 10,047 (31.6 $\mu$M) gave dose-ratios obtained from Schild plots of 4.5 and 8.3 respectively, and when superfused together, their effects appeared additive since the dose-ratio was 12.2 (see Fig. 4).

## DISCUSSION

The present experiments demonstrate that the dissociative anaesthetics, sigma opiates and MK-801 are able to

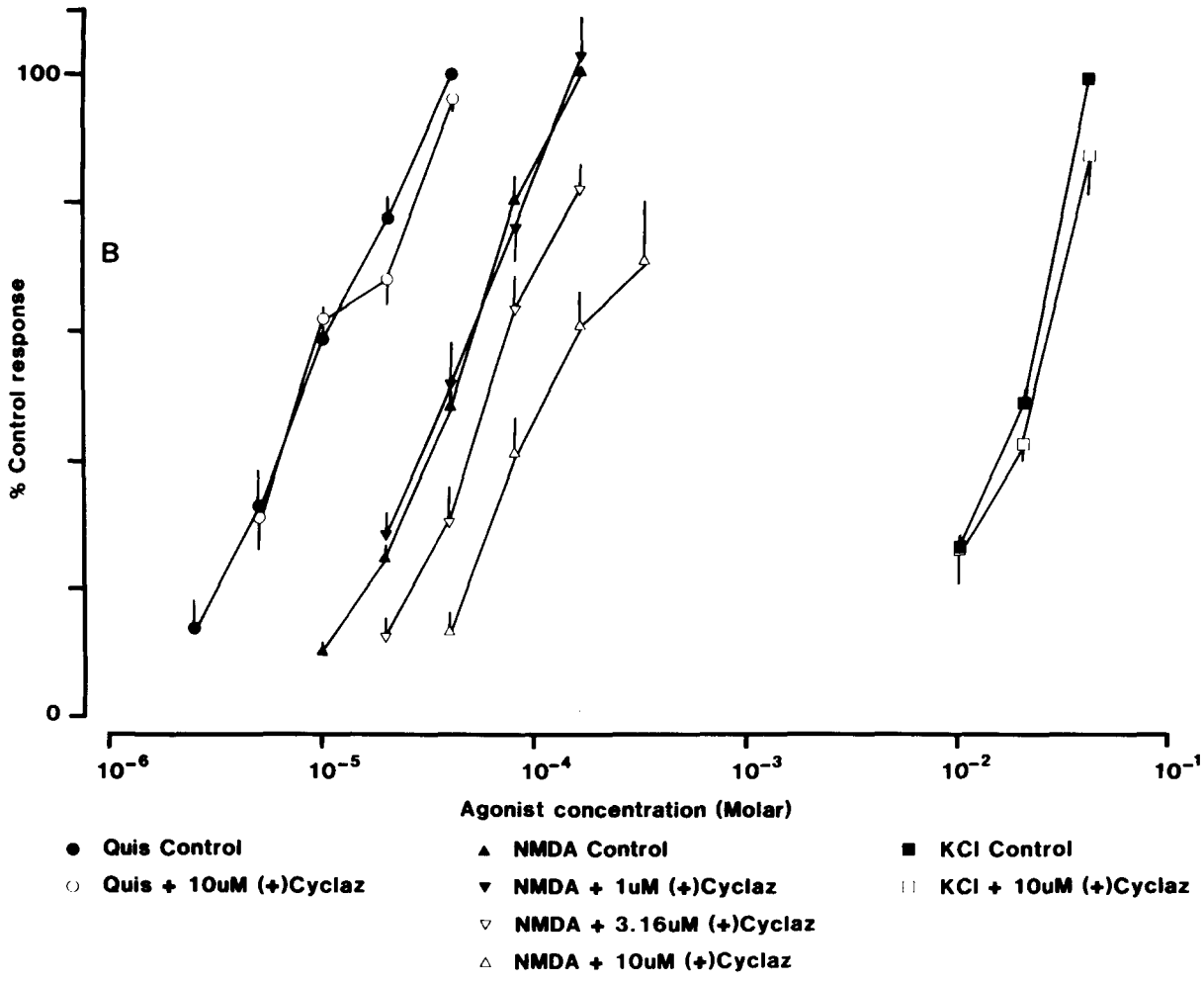


FIG. 3. Selective effect of (+) cyclazocine as an NMDA antagonist on spinal motoneurones of the frog. Each point on the dose-response curve represents the mean result from at least four hemisected spinal cords and the vertical bars indicate the S.E.M. Responses for each agonist are normalised by expressing the results as a percentage of the control response to 40 $\mu$M quisqualate, 40 $\mu$M NMDA or 40 mM KCl.

selectively reduce depolarisations of cortical and spinal neurones induced by NMDA while having little or no effect on kainate and quisqualate responses. Depression of NMDA responses was stereoselective and dose-dependent, although in mose cases full recovery except with ketamine was not obtained. These electrophysiological findings are in agreement with other in vitro studies (16, 27, 36).

The noncompetitive nature of ketamine as an antagonist of NMDA-induced depolarisations (16,36) and NMDA-stimulated transmitter release (32,46) was confirmed and combination studies further suggest that SKF 10,047 and ketamine act at the same site. The proposal (36) that this site is distinct from those of competitive antagonists and of magnesium has received support from binding studies in which ketamine did not displace [$^3$H]-2-AP5 binding (54) and in which both NMDA and magnesium enhanced, rather than reduced, binding at the PCP receptor (12, 14, 24, 33). Nevertheless, at low doses, these compounds often gave parallel shifts in the NMDA dose-response curves. This apparent anomaly may be explained by failure to achieve full equilibrium (23) or by the presence of spare receptors for NMDA (16).

The marked stereoselectivity of PCMP and the weak and variable stereoselectivity of benzomorphans as NMDA antagonists is also in agreement with the pharmacology of PCP in both binding (38, 41, 42) and behavioural studies (4, 43, 59), but is quite different from stereoselectivity at the sigma site (10,28). Furthermore, the sigma receptor ligand, haloperidol, as well as mu and kappa opiates, had no selective effect on NMDA, a finding consistent with in vitro microelectrophoretic studies (31,39). Thus, actions at sigma, mu or kappa receptors do not underlie the NMDA antagonist properties of dissociative anaesthetics and sigma opiates.

Structure-activity relationships (SAR) of PCP receptor agonists have been studied extensively using binding assays (15, 38, 41, 52, 58, 59). This same SAR satisfies NMDA antagonism by PCP-like compounds because when relative potencies (Table 2) are compared, a Spearman rank correlation coefficient of $>.8$ ($p<0.025$) is obtained. It is particularly clear from those studies where both PCP and sigma

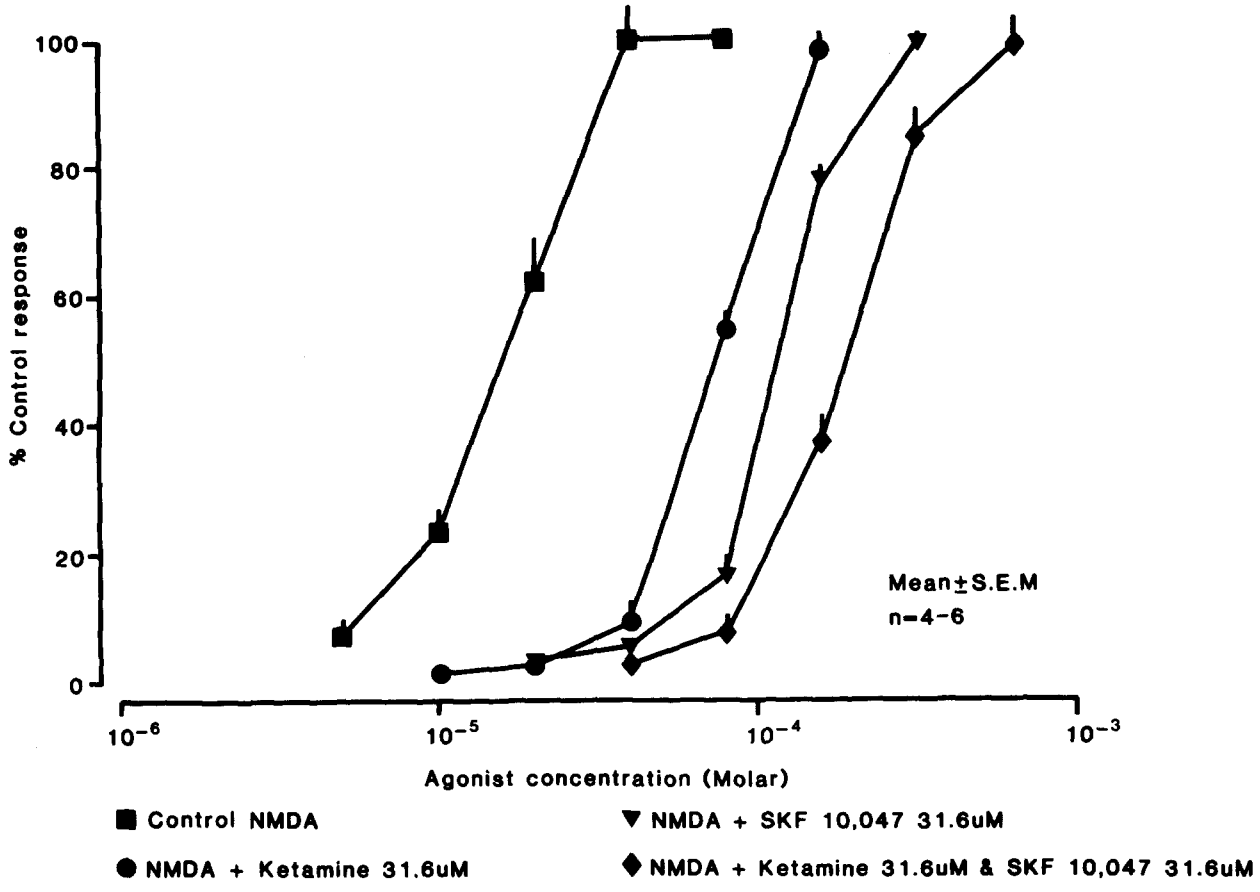


FIG. 4. Effects of 31.6 $\mu$M ketamine and SKF 10,047 either singly or in combination on dose-response curves to NMDA on rat cortical wedges. It can be seen that when added together these two antagonists produced an additive shift of the dose-response curve to the right. If the two substances had been acting at separate sites, an $ED_{50}$ for NMDA in the presence of the two would have been predicted to be almost 1 mM. Each data point represents the mean ± S.E.M. of results from at least 4 preparations.

TABLE 1

POTENCY OF PHENCYCLIDINE-LIKE COMPOUNDS AS NMDA ANTAGONISTS IN VITRO

| | Rat Cortical Wedges $IC_{50}$ ($\mu$M) | Hemisected Frog Cords $IC_{50}$ ($\mu$M) |
|---|---|---|
| MK-801 | 0.2 ± 0.03 | 3.5 ± 0.8 |
| TCP | 0.9 ± 0.1 | NT |
| (−) Cyclazocine | 1.1 ± 0.15 | 5.7 ± 1.0 |
| PCP | 1.7 ± 0.2 | 5.4 ± 0.9 |
| (+) PCMP | 2.5 ± 0.2 | 2.1 ± 0.3 |
| (+) SKF 10,047 | 4.0 ± 0.3 | 9.3 ± 0.7 |
| (+) Cyclazocine | 4.7 ± 0.5 | 8.3 ± 2.4 |
| Ketamine | 11.6 ± 2.5 | 8.9 ± 0.8 |
| (−) SKF 10,047 | 22.5 ± 1.2 | 29.7 ± 3.1 |
| (−) PCMP | 28.7 ± 3.9 | 33.4 ± 4.3 |

$IC_{50}$ values (mean ± S.E.M.) were calculated for inhibition of depolarisations induced by 40 $\mu$M NMDA on not less than 4 preparations. (NT—not tested). The following drugs were inactive as NMDA antagonists (the maximum concentration tested is given in parentheses): morphine (100 $\mu$M), U50,488H (100 $\mu$M), tifluadom (10 $\mu$M), naloxone (10 $\mu$M), haloperidol (100 $\mu$M).

binding were studied in parallel (10, 28, 45), that NMDA antagonism only correlates with potency at the PCP receptor. Only with MK-801 is there wide deviation between the different assays in part due to the use- and temperature-dependence of its block of NMDA (7,56).

Thus, it is apparent that PCP receptors mediate the NMDA antagonist effect of dissociative anaesthetics, sigma opiates and related compounds.

Is NMDA antagonism also responsible for the behavioural effects of these compounds? In drug discrimination studies, animals do not distinguish between dissociative anaesthetics and the sigma opiates, especially if any mu and kappa properties of the sigma opiates are blocked by naloxone (3, 17, 18, 43, 44). Relative potencies in these behavioural studies are similar to those at the PCP receptor (38, 47, 58, 59). A good correlation was found between the rank order potencies of drugs tested in these studies as NMDA antagonists and for the PCP-like discrimination stimulus properties ($r=.95$; $p<0.01$). Similar correlations ($r>.9$ exist between NMA antagonism and PCP-induced catalepsy in the pigeon (39). This is consistent with the hypothesis that reduced excitatory transmission utilizing NMDA receptors underlies some of the behavioural properties common to

TABLE 2

RELATIVE POTENCIES OF PHENCYCLIDINE-LIKE COMPOUNDS IN ELECTROPHYSIOLOGICAL, BIOCHEMICAL AND BEHAVIOURAL TESTS

| | As NMDA Antagonists | | | | | |
|---|---|---|---|---|---|---|
| | Cortex In Vitro | Cord In Vitro | Cord* In Vivo | PCP[2]† Binding | PCP‡ Discrim-ination | PCP[4]§ Catalepsy |
| MK-801 | 8.5 | 1.5 | 3.5 | 30 | 3–10 | 3.2 |
| TCP | 1.88 | NT | 1.7 | 1.57 | 1.46 | NT |
| (−) CYC | 1.54 | 0.95 | 0.8 | 0.36 | 1.09 | 2.0 |
| PCP | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| (+) PCMP | 0.69 | 2.6 | 1.2 | NT | 1.0 | NT |
| (+) SKF | 0.43 | 0.58 | 0.3 | 0.2 | 0.45 | 0.25 |
| (+) CYC | 0.36 | 0.65 | 0.4 | 0.1 | 0.13 | 0.5 |
| (±) KET | 0.15 | 0.6 | 0.1 | 0.15 | 0.10 | 0.25 |
| (−) SKF | 0.08 | 0.18 | 0.2 | 0.18 | 0.18 | 0.25 |
| (−) PCMP | 0.06 | 0.16 | 0.1 | NT | 0.3 | NT |

Potencies of drugs in pharmacological, binding and behavioural studies are expressed relative to that of PCP. Other compounds, e.g., naloxone, morphine, U50,488H, haloperidol were inactive in these tests. NT—not tested.

*Values compiled from (2, 7, 29, 31) and cited papers.

†Values compiled from references (15, 38, 41, 57–59) [except MK-801 which is from (56) for displacement of $^3$H-MK-801 binding].

‡Values from (43) [except MK-801 from (20,26)].

§Values from (38) [except MK-801 from (26)].

these drugs. One of the implications from this is that NMDA antagonists of the competitive type should also have PCP-like properties. In support of this hypothesis is the finding that DL-AP5 produces PCP-like discrimination stimulus effects (20,26) and PCP-like catalepsy in pigeons (25). How much such correlations are predictive of psychotomimetic activity in man remains to be determined.

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