Pharmacology Biochemistry & Behavior, Vol. 36, pp. 111–115. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

The Noncompetitive N-Methyl-D-Aspartate Antagonists, MK-801, Phencyclidine and Ketamine, Increase the Potency of General Anesthetics

LAURA C. DANIELL

Department of Pharmacology and Toxicology, Medical College of Georgia, Augusta, GA 30912-2300

Received 18 October 1989

DANIELL, L. C. *The noncompetitive N-methyl-D-aspartate antagonists, MK-801, phencyclidine and ketamine, increase the potency of general anesthetics.* PHARMACOL BIOCHEM BEHAV **36**(1) 111–115, 1990.—The potency of general anesthetics from different chemical classes was tested after pretreatment with subanesthetic doses of noncompetitive N-methyl-D-aspartate (NMDA) antagonists in mice. Changes in general anesthetic potency were assessed by determination of alteration of duration of loss of righting reflex for ethanol and pentobarbital and changes in the mimimum alveolar concentration (MAC) for the volatile anesthetics, halothane and diethyl ether. The ability of the noncompetitive NMDA antagonists, MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine], phencyclidine (PCP) and ketamine, to increase the potency of general anesthetics paralleled their potency as NMDA antagonists and their affinity for the PCP receptor site of the NMDA receptor-ionophore complex (MK-801 > PCP > ketamine). These results indicate that block of central NMDA receptors may contribute to the production of anesthesia by a variety of agents.

MK-801 Phencyclidine Ketamine NMDA Anesthetics Ethanol Barbiturates Halothane Diethyl ether Minimum alveolar concentration Behavior

PCP was developed for use as a dissociative anesthetic. In humans, low doses of the drug produce a combination of stimulant and depressant behaviors including various psychotomimetic and euphoric effects while higher doses produce an anesthetic state characterized by analgesia and dissociation from environmental stimuli (3). In rodents, the drug increases locomotion and stereotypic behavior and has anticonflict and anticonvulsant effects. At higher doses, PCP produces ataxia and anesthesia (4,15). Ketamine, with somewhat reduced psychotomimetic effects, is less potent than PCP and is in current clinical use (32).

MK-801 is an anticonvulsant which produces behavioral responses similar to those elicited by PCP but is approximately 10 times more potent (16). Recent studies have shown that MK-801, PCP and ketamine are noncompetitive antagonists at glutamate receptors selectively activated by NMDA (1, 6, 8, 16) and bind to a site labelled by PCP and MK-801 (10, 23, 28). Competitive NMDA-receptor antagonists such as 2-amino-5-phosphonopentanoic acid produce qualitatively similar PCP-like behaviors (15). These results suggest that antagonism of NMDA-mediated neurotransmission is associated with PCP-like behavioral effects and dissociative anesthesia.

General anesthetics depress excitatory neurotransmission in central neurons. At concentrations which are pharmacologically relevant, these agents inhibit transmission by acting at presynaptic and/or postsynaptic sites rather than by inhibiting axonal impulse conduction (2, 17, 24). These results indicate that anesthesia could be produced by effects on particular receptor sites. However, the role of specific sites of anesthetic action in brain tissue has not been identified. Previous work, however, showed that general anesthetics inhibit glutamate responses in central neurons (5, 11, 34). Other work showed that pretreatment with PCP increases the effects of general anesthetics on depressant and operant behaviors (6, 29–31). These studies indicate that general anesthetics may interact at a site or sites of the NMDA receptor.

In this study, I compared the effects of pretreatment with compounds active at the PCP site of the NMDA receptor on the potency of general anesthetics from different chemical classes. My results indicate that block of NMDA-mediated neurotransmission contributes to the production of anesthesia by chemically diverse agents.

METHOD

Materials

Male ICR mice (Harlan) 55 to 90 days old were used in all experiments. (+)-MK-801 was a gift of Merck Sharpe and Dohme. Ketamine was a gift of Parke-Davis. PCP was obtained as the hydrochloride salt from Research Biochemicals. Pentobarbital was obtained from Sigma Chemical Co. Halothane was from Ayerst Laboratories, Inc. and diethyl ether was obtained from

Fisher. All other chemicals used were of the highest grade. With the exception of halothane and diethylether, all drugs were dissolved in saline.

Determination of Duration of Ethanol and Pentobarbital-Induced Anesthesia

Hypnotic doses of ethanol (4.2 g/kg, 25% w/v solution) or pentobarbital (45 or 50 mg/kg) were administered intraperitoneally (IP) 30 min after IP administration of MK-801, PCP or ketamine. Duration of anesthesia was defined as the time from ethanol or pentobarbital administration to regaining of righting reflex. Loss of righting reflex typically occurred within 2 min following ethanol administration and 7 min following pentobarbital administration.

Determination of MAC of Diethylether and Halothane

MAC was determined by measurement of the responsiveness to an aversive stimulus of fractions of small groups of mice at successively increased anesthetic concentrations. Group of six or eight mice were placed in an airtight Plexiglas box of dimensions 66 cm wide × 29 cm deep × 30 cm high. Volatile anesthetics mixed with air entered the box at one end and were vented at the other end. MAC determination was begun 15 min after administration of MK-801, PCP or ketamine. After equilibration with each inspired concentration of anesthetic for 15 min, animals were tested for responsiveness to stimulus. These determinations of inspired anesthetic concentration were not corrected for the slight reduction which occurred during testing for responsiveness to stimulus. The stimulus consisted of a hemostat clamp placed 2 cm from the distal end of the tail adjusted to the first notch for 30 sec. Responsiveness was defined as purposeful movement and did not include reflexive increases in respiration. Each group of animals was treated as a single experiment. The MAC value for each experiment was obtained by least squares linear regression analysis of fractional responsiveness data for the different volatile anesthetic concentrations tested.

Statistics

The data were analyzed by one-way analysis of variance.

RESULTS

Behavioral Effects of MK-801, PCP and Ketamine Alone

MK-801 and PCP produced similar behaviors. Low doses of MK-801 (1.0 mg/kg, IP) and PCP (1.0 mg/kg, IP) produced increased locomotion, wild running, Straub tail, jumping and stereotypic movements (sniffing, etc). Slightly higher doses (MK-801: 3 mg/kg, IP; PCP: 10 mg/kg, IP) produced ataxia and swaying movements in concert with increased locomotor activity and stereotypic behavior. The lowest dose of MK-801 tested (0.3 mg/kg, IP) did not produce any observable behavioral effects. Ketamine (10 and 30 mg/kg, IP) produced similar effects. However, ketamine-induced increases in locomotor activity and stereotypic behavior were less pronounced than increases produced by PCP or MK-801.

Doses of MK-801 (50 mg/kg, IP) and PCP (50 mg/kg, IP) considerably higher than those used in pretreatment studies (below) produced severe ataxia but did not result in loss of righting reflex. At these doses, increases in locomotor and stereotypic activity were also evident. Ketamine generally produced loss of righting reflex at a dose of 100 mg/kg, IP.

Effect of MK-801, PCP and Ketamine Pretreatment on the Duration of Ethanol and Pentobarbital Anesthesia

The duration of ethanol- and pentobarbital-induced anesthesia was measured from the time of drug administration to regaining of righting reflex. Duration of ethanol and pentobarbital-induced loss of righting reflex was increased by drug pretreatment with the following order of potency: MK-801 > PCP > ketamine (Figs. 1, 2, 3). Duration of ethanol-induced anesthesia appeared to be somewhat more sensitive to MK-801 pretreatment than pentobarbital anesthesia. The largest dose of MK-801 tested, 3 mg/kg, produced a 593 and 233% increase in the duration of ethanol and pentobarbital anesthesia, respectively. The largest dose of PCP tested, 10 mg/kg, increased the duration of ethanol and pentobarbital anesthesia by 159 and 39%, respectively (Fig. 2). Ketamine increased the duration of pentobarbital but not ethanol anesthesia at doses of 10 and 30 mg/kg. However, the increase produced by ketamine was less marked than for MK-801 pretreatment, amounting to a 50% increase in the duration of pentobarbital anesthesia after treatment with the highest dose of ketamine tested in these experiments (30 mg/kg, IP) (Fig. 3). Observation of animals used in these experiments approximately 20 hours after regaining righting reflex revealed no gross behavioral changes and no lethalities.

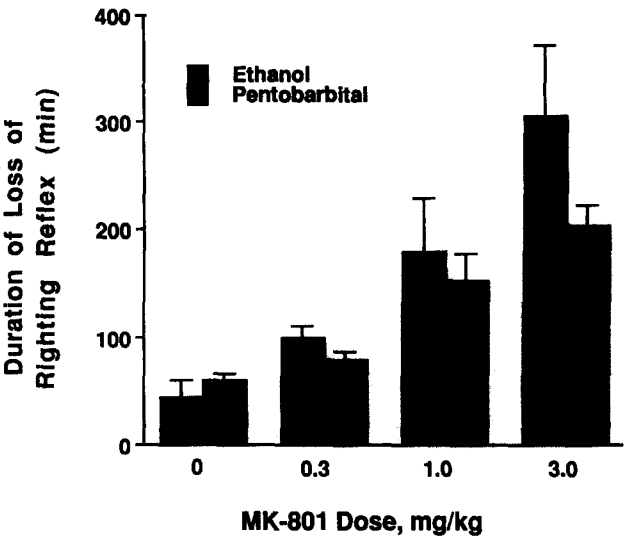

FIG. 1. The effect of MK-801 pretreatment on the duration of loss of righting reflex due to ethanol (4.2 g/kg, IP) or pentobarbital (50 mg/kg, IP). Various doses of MK-801 were administered IP 30 min before ethanol or pentobarbital. Data are the means ± SE for 6, 7 or 8 animals (ethanol experiments) or 8 animals (pentobarbital experiments) at each MK-801 dose. The data were analyzed by one-way ANOVA with the following results: for ethanol, $F(3,27) = 25.5$, $p<0.0001$; for pentobarbital, $F(3,31) = 24.4$, $p<0.00001$.

Effect of Pretreatment With MK-801 and PCP on the MAC of Volatile Anesthetics

The MAC for halothane and diethyl ether was measured after pretreatment with MK-801 or PCP. Doses of MK-801 (0.3 to 3 mg/kg, IP) which increased the duration of ethanol and pentobarbital anesthesia reduced the halothane MAC in a dose-dependent manner (Table 1). PCP also reduced the MAC for halothane but was at least 10 times less potent than MK-801 (Table 1). Similarly, MK-801 reduced the MAC for diethyl ether (Table 2). PCP also reduced the diethyl ether MAC but was less potent than MK-801 (Table 2). MK-801 and PCP produced a maximal reduction of approximately 40% in the MAC values for both

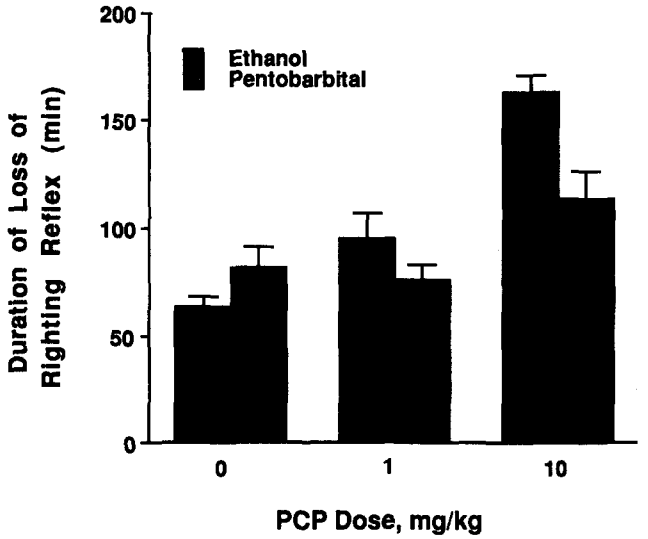

FIG. 2. The effect of PCP pretreatment on the duration of loss of righting reflex due to ethanol (4.2 g/kg, IP) or pentobarbital (45 mg/kg, IP). Various doses of MK-801 were administered IP 30 min before ethanol or pentobarbital. Data are the means ± SE of 8 (saline, 1 mg/kg PCP) or 4 animals (10 mg/kg PCP) for ethanol experiments or 8 to 11 animals for pentobarbital experiments. The data were analyzed by one-way ANOVA with these results: for ethanol, $F(2,19)=22.3$, $p<0.0001$; for pentobarbital, $F(2,29)=4.4$, $p<0.05$.

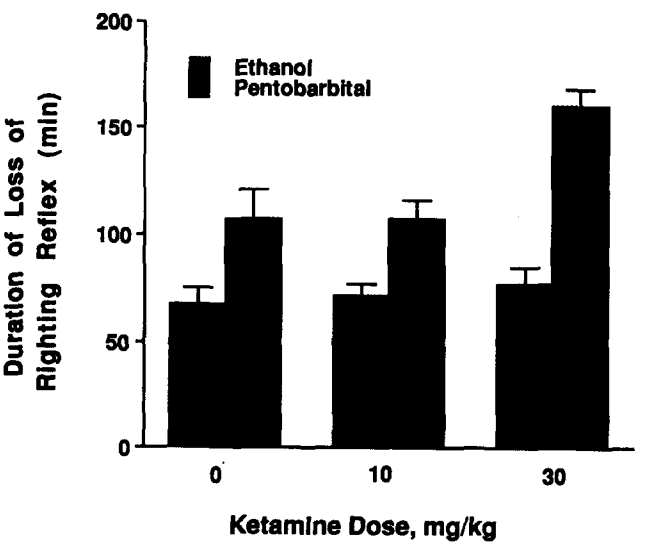

FIG. 3. The effect of ketamine pretreatment on the duration of loss of righting reflex due to ethanol (4.2 g/kg, IP) or pentobarbital (45 mg/kg, IP). Various doses of MK-801 were administered IP 30 min before ethanol or pentobarbital. Data are the means ± SE of 9 or 10 animals for ethanol experiments and 4 or 5 animals for pentobarbital experiments. The data were analyzed by one-way ANOVA with these results: for ethanol, $F(2,28)=0.44$, $p<0.65$; for pentobarbital, $F(2,13)=8.2$, $p<0.01$.

TABLE 1

EFFECT OF MK-801 AND PCP ON HALOTHANE MAC

Pretreatment	Dose (mg/kg, IP)	MAC (%)	% Reduction of MAC	n
Saline	—	0.77 ± 0.02	—	3
MK-801	0.3	0.57 ± 0.01	26	3
MK-801	1.0	0.51 ± 0.04	34	3
MK-801	3.0	0.44 ± 0.03	43	3
Saline	—	0.88 ± 0.01	—	2
PCP	1.0	0.83 ± 0.01	6	2
PCP	10.0	0.65 ± 0.01	26	2

Mice were pretreated with saline, MK-801 or PCP 15 min before measurement of halothane MAC. Data are the means ± SE of 2 or 3 experiments, as indicated. The data were analyzed by one-way ANOVA with the following results: for MK-801 pretreatment, $F(3,11)=30.9$, $p=0.0001$; for PCP pretreatment, $F(2,5)=126.9$, $p=0.001$.

halothane and diethyl ether (Tables 1 and 2).

DISCUSSION

The potency of general anesthetics may be modified by pretreatment with various drugs. Determination of reduction of the MAC of volatile anesthetic agents by drug pretreatment is a standard method for measurement of anesthetic potency (9). Other work also provided evidence that the duration of anesthesia following drug pretreatment is related to anesthetic potency (12). The ability of drug pretreatments to alter anesthetic potency can provide evidence for specific sites of action of general anesthetics.

My results show that the potency or duration of action of general anesthetics, selected from different chemical classes, can be increased by pretreatment with subanesthetic doses of drugs active at the PCP site of the NMDA receptor. These results agree with a recent study, published while this manuscript was in preparation, which showed that the potency of the volatile anesthetics, halothane and isoflurane, is increased by pretreatment with MK-801 (27). The doses of MK-801 (0.3 to 3 mg/kg IP) and PCP (1 and 10 mg/kg, IP) used in this study are considerably smaller than anesthetic doses of these agents (>50 mg/kg, IP) in male ICR mice. My results show that relatively low doses of MK-801 (0.3

TABLE 2

EFFECT OF MK-801 AND PCP ON DIETHYL ETHER MAC

Pretreatment	Dose (mg/kg, IP)	MAC (%)	% Reduction of MAC	n
Saline	—	6.4 ± 0.4	—	3
MK-801	0.3	5.1 ± 0.2	20	3
MK-801	1.0	3.9 ± 0.2	39	3
MK-801	3.0	4.1 ± 0.2	36	3
Saline	—	5.7 ± 0.1	—	2
PCP	1.0	5.7 ± 0.1	0	2
PCP	10.0	5.1 ± 0.1	11	2

Mice were pretreated with saline, MK-801 or PCP 15 min prior to measurement of diethylether MAC. MAC values are the means ± SE of 2 or 3 experiments, as indicated. The data were analyzed by one-way ANOVA with the following results: for MK-801 pretreatment, $F(3,11)=22.3$, $p=0.0003$; for PCP pretreatment, $F(2,5)=10.0$, $p=0.047$.

and 1.0 mg/kg, IP) produce large increases in the duration of ethanol and pentobarbital anesthesia and strongly potentiate the anesthetic effects of the general anesthetics tested in this study. The ability of these NMDA antagonists to increase the potency of general anesthetics parallels their potency as displacers of ligands specific for the NMDA receptor (10, 23, 28). The order of potency of PCP-like ligands observed in this study also follows that of in vitro studies of antagonism of NMDA responses (33) and of NMDA-mediated effects in vivo (convulsions and neurotoxicity) (7,22).

The findings of this study are supported by work which showed that PCP increases the behavioral effects of general anesthetics. Previous studies showed that low doses of PCP increase the duration of ethanol and hexobarbital-induced loss of righting reflex (6,29) and increased the motor-incoordinating effects of ethanol (6). In addition, ethanol and pentobarbital potentiate the PCP-induced disruption of operant behaviors in rodents (30,31).

Several possibilities exist for the mechanism of NMDA-antagonist-induced potentiation of anesthetic potency. Block of brain NMDA receptor sites could contribute to the production of anesthesia by a mechanism unrelated to the basic mechanism of action of the general anesthetics themselves. Further, the potentiation of general anesthetic potency by NMDA receptor antagonists would not necessarily imply any common mechanism of action of general anesthetics. In that case, it is expected that NMDA receptor antagonists could, at sufficiently high doses, produce anesthesia in the absence of administration of any other agents. In fact, this is true for each of the NMDA antagonists examined in the study. However, the fact that much larger doses of these NMDA antagonists are required for the production of anesthesia in the absence of other agents than for the potentiation of the anesthetic potency of a variety of general anesthetics (more than 50 times higher in the case of MK-801) argues against this possibility.

Alternatively, general anesthetics may interact specifically with a recognition site of the NMDA receptor. General anesthetics could interact with a number of different sites of the NMDA receptor, any of which would reduce NMDA-mediated neurotransmission, and enhance anesthetic potency. The functional expression of the NMDA receptor is modified by the binding of glycine, an allosteric modulator of agonist binding, and by Mg and PCP, both of which appear to bind to sites inside the NMDA-operated cation channel (20,23). My results suggest that general anesthetics may interact with the MK-801/PCP site of the NMDA receptor-ionophore complex. However, the interactions between the various binding sites of the NMDA receptor are complex and alteration of binding of a ligand at one site can alter ligand binding at another site of the NMDA receptor (23). Previous work showed that glycine enhances the binding of MK-801 (23), indicating that general anesthetics could interact with this site of the NMDA receptor.

The idea that block of the NMDA receptor may, in part, mediate the action of general anesthetics is supported by previous work which demonstrated that general anesthetics block glutaminergic stimulation of central neurons (5, 21, 25, 26). Recent work showed that ethanol blocks NMDA-activated ionic currents in hippocampal neurons (18, 19, 21). This effect was also produced by a series of anesthetic n-alcohols and was correlated with their motor-incoordinating actions (19). In addition, NMDA-stimulated increases in calcium uptake and cyclic guanosine monophosphate (cGMP) in central neurons are reduced by incubation with ethanol (13). In that study, ethanol appeared to reduce NMDA-mediated cGMP production by inhibition of glycine-mediated stimulation rather than by an effect at the PCP site of the NMDA receptor (13). Further work will be required to determine whether other general anesthetics produce similar effects in vitro and whether these actions are related to the production of anesthesia by chemically diverse agents.

MK-801 and PCP produced a maximal or limiting reduction of approximately 40% in the MAC of halothane and diethyl ether. This result suggests that actions at brain sites other than the NMDA receptor could also mediate the effects of general anesthetics. Other work showed that stimulation of GABA-mediated neurotransmission may be involved in anesthesia (14). The balance of anesthetic-induced stimulation of GABA-mediated inhibitory neurotransmission and reduction of NMDA-mediated excitatory neurotransmission may underlie the central actions of general anesthetics. This possibility is particularly interesting in view of the apparent similarity in complexity of allosteric modulation of the NMDA and GABA receptor/ionophore complexes.

In conclusion, these results suggest that block of NMDA receptors contributes to the production of anesthesia by several different general anesthetic agents. Although a precise mechanism of enhancement of general anesthetic potency by NMDA antagonists is not clear at present, these findings may have relevance for the development of novel anesthetic agents.

ACKNOWLEDGEMENTS

This work was supported by the Medical College of Georgia Research Institute and the Alcoholic Beverage Medical Research Foundation.

REFERENCES

1. Anis, N. A.; Berry, S. C.; Burton, N. R.; Lodge, D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br. J. Pharmacol. 79:565–575; 1983.
2. Austin, G. M.; Pask, E. A. Effect of ether inhalation upon spinal cord and root action potentials. J. Physiol. 118:405–411; 1952.
3. Balster, R. L. Clinical implications of behavioral pharmacology research on phencyclidine. In: Clouet, D. H., ed. Phencyclidine: An update. Rockville, MD: Public Health Service; 1986:148–162.
4. Balster, R. L.; Chait, L. D. The behavioral effects of phencyclidine in animals. In: Petersen, R. C.; Stillman, R. C., eds. Phencyclidine abuse: An appraisal (NIDA Monograph). Rockville, MD: Public Health Service; 1978:53–65.
5. Barker, J. L.; Ransom, B. R. Pentobarbitone pharmacology of mammalian central neurons grown in tissue culture. J. Physiol. 280:355–372; 1978.
6. Brunet, B. L.; Reifferstein, R. J.; Williams, T.; Wong, L. Toxicity of phencyclidine and ethanol in combination. Alcohol Drug Res. 6: 341–349; 1986.
7. Buterbaugh, G. G.; Michelson, H. B. Anticonvulsant properties of phencyclidine and ketamine. In: Clouet, D. H., ed. Phencyclidine: An update. Rockville, MD: Public Health Service; 1986:67–79.
8. Drejer, J.; Honore, T. Phencyclidine analogues inhibit NMDA-stimulated [3H]GABA release from cultured cortex neurons. Eur. J. Pharmacol. 143:287–290; 1987.
9. Eger, E. I.; Saidman, L. J.; Brandstater, B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 26:756–763; 1965.
10. Foster, A. C.; Wong, E. H. F. The novel anticonvulsant MK-801 binds to the activated state of the N-methyl-D-aspartate receptor in rat brain. Br. J. Pharmacol. 91:403–409; 1987.
11. Franklin, C. L.; Gruol, D. L. Acute ethanol alters the firing pattern and glutamate response of cerebellar Purkinje neurons in culture. Brain Res. 416:205–218; 1987.
12. Gessner, P. K.; Cabana, B. E. A study of the interaction of the hypnotic effects and the toxic effects of chloral hydrate and ethanol. J. Pharmacol. Exp. Ther. 174:247–259; 1970.
13. Hoffman, P. L.; Rabe, C. S.; Moses, F.; Tabakoff, B. N-Methyl-

D-asapartate receptors and ethanol: inhibition of calcium flux and cyclic GMP production. J. Neurochem. 52:1937–1940; 1989.
14. Huidobro-Toro, J. P.; Bleck, V.; Allan, A. M.; Harris, R. A. Neurochemical actions of anesthetic drugs on the gamma-aminobutyric acid receptor-chloride channel complex. J. Pharmacol. Exp. Ther. 242:963–969; 1987.
15. Koek, W.; Woods, J. H. Assessing directly observable behavioral effects of phencyclidine (PCP)-like drugs in pigeons, in rats, and in rhesus monkeys. In: Domino, E. F.; Kamenka, J. M., ed. Sigma and phencyclidine-like compounds as molecular probes in biology. Ann Arbor, MI: NPP Books; 1988:493–509.
16. Koek, W.; Woods, J. H.; Winger, G. D. MK-801, a proposed non-competitive antagonist of excitatory amino acid neurotransmission, produces phencyclidine-like behavioral effects in pigeons, rats and rhesus monkeys. J. Pharmacol. Exp. Ther. 245:969–974; 1988.
17. Larrabee, M. G.; Posternak, J. M. Selective action of anesthetics on synapses and axons in mammalian sympathetic ganglia. J. Neurophysiol. 15:91–114; 1952.
18. Lima-Landman, M. T. R.; Albuquerque, E. X. Ethanol potentiates and blocks NMDA-activated single-channel currents in rat hippocampal pyramidal cells. FEBS Lett. 247:61–67; 1989.
19. Lovinger, D. M.; White, G.; Weight, F. F. Ethanol inhibits NMDA-activated ion current in hippocampal neurons. Science 243:1721–1724; 1989.
20. Mayer, M. L.; Westbrook, G. L.; Vyklicky, L. Sites of antagonist action on N-methyl-D-aspartic acid receptors studied using fluctuation analysis and a rapid perfusion technique. J. Neurophysiol. 60: 645–663; 1988.
21. Nicoll, R. A.; Wojtowicz, J. M. The effects of pentobarbital and related compounds on frog motoneurons. Brain Res. 191:225–237; 1980.
22. Olney, J. W.; Price, M. T.; Fuller, T. A., *et al.* The anti-excitotoxic effects of certain anesthetics, analgesics and sedative-hypnotics. Neurosci. Lett. 68:29–34; 1986.
23. Reynolds, I. J.; Miller, R. J. Multiple sites for the regulation of the N-methyl-D-aspartate receptor. Mol. Pharmacol. 33:581–584; 1988.
24. Richards, C. D.; Russell, W. J.; Smaje, J. C. The action of ether and methoxyflurane on synaptic transmission in siolated preparation of the mammalian cortex. J. Physiol. 248:121–142; 1975.
25. Richards, C. D.; Smaje, J. C. Anesthetics depress the sensitivity of cortical neurons to L-glutamate. Br. J. Pharmacol. 58:347–357; 1976.
26. Richter, J.; Landau, E. M.; Cohen, S. Anaesthetic and convulsant ethers act on different sites at the crab neuromuscular junction in vitro. Nature 266:70–71; 1977.
27. Scheller, M. S.; Zornow, M. H.; Fleischer, J. E.; Shearman, G. T.; Greber, T. F. The noncompetitive N-methyl-D-aspartate receptor antagonist, MK-801, profoundly reduces volatile anesthetic requirements in rabbits. Neuropharmacology 28:677–681; 1989.
28. Sircar, R.; Rappaport, M.; Nichtenhauser, R.; Zukin, S. R. The novel anticonvulsant MK-801: a potent and specific ligand of the brain phencyclidine/σ-receptor. Brain Res. 435:235–240; 1987.
29. Stone, C. J.; Forney, R. B. The effects of phencyclidine on ethanol and sodium hexobarbital in mice. Toxicol. Appl. Pharmacol. 40: 177–183; 1977.
30. Thompson, D. M.; Moerschbaecher, J. M. Phencyclidine in combination with pentobarbital: Supra-additive effects on complex operant behavior in Patas monkey. Pharmacol. Biochem. Behav. 16:159–165; 1982.
31. Wessinger, W. D.; Balster, R. L. Interactions between phencyclidine and central nervous system depressants evaluated in mice and rats. Pharmacol. Biochem. Behav. 27:323–332; 1987.
32. Winters, W. D.; Ferrer-Allado, T.; Guzman-Flores, C. The cataleptic state produced by ketamine: a review of the neuropharmacology of anesthesia. Neuropharmacology 11:303–315; 1972.
33. Wong, E. H. F.; Kemp, J. A.; Prietley, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. Proc. Natl. Acad. Sci. USA 83: 7104–7108; 1986.
34. Yool, A. J.; Gruol, D. L. Development of spontaneous and glutamate-evoked activity is altered by chronic ethanol in cultured cerebellar Purkinje neurons. Brain Res. 420:205–219; 1987.