

Ketamine Blocks the Plasticity Associated With Prefrontal Cortex Self-Stimulation

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CORBETT, D. *Ketamine blocks the plasticity associated with prefrontal cortex self-stimulation.* PHARMACOL BIOCHEM BEHAV 37(4) 685–688, 1990.—Intracranial self-stimulation (ICSS) at sites within the medial prefrontal cortex (MFC) is acquired slowly but can be hastened by prior exposure to a regimen of noncontingent stimulation delivered to the MFC ICSS electrode. The facilitatory effects of noncontingent MFC stimulation on subsequent ICSS acquisition were blocked by pretreatment with ketamine, a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. These findings provide further support for the view that the NMDA receptor is importantly involved in mechanisms of neural plasticity.

NMDA Neuronal plasticity Reward Prefrontal cortex Kindling

THE N-methyl-D-aspartate (NMDA) receptor has been implicated in various forms of neuronal plasticity including: long-term potentiation (LTP), kindling and spatial learning. For example, NMDA receptor antagonists have been reported to block the formation of LTP but not to interfere with its expression (4, 8, 21). Similar results have been noted with kindling where NMDA antagonists retard the development of amygdala or electroshock kindling (2, 3, 10, 18). However, the most interesting effects of NMDA receptor blockade are those demonstrating an interference with learning. Morris was the first to show that an NMDA antagonist selectively interfered with acquisition of place learning in the Morris water maze (19). Since then, there have been numerous studies involving NMDA antagonists that have demonstrated learning impairments in: spatial or place tasks (12, 29, 30); passive avoidance tests (1,25), but not cue or visual discrimination tests (20,25). Since kindling and LTP share many characteristics and have both been suggested to represent models of learning and memory (3), it is not surprising that they appear to rely, at least in part, upon the same mechanism (i.e., NMDA activation) for their development. However, other types of neuroplasticity with less apparent relation to learning also appear to utilize the NMDA receptor. For instance, the shift in ocular-dominance during the critical period of visual system development as the result of monocular occlusion can be attenuated by intracortical infusion of an NMDA antagonist (11). These latter findings suggest that the NMDA receptor may participate generally in many different types of neuroplasticity.

An interesting type of plasticity is also associated with ICSS in the prefrontal cortex. Self-stimulation in this brain region is typically acquired very slowly, taking 4–6 days to develop. The acquisition of prefrontal ICSS can be facilitated by pretreatment with noncontingent stimulation prior to lever-press training (5,23). This pretreatment effect is similar to the potentiation characteristic of LTP and kindling and thus may also involve the NMDA

receptor. If this hypothesis is correct then an NMDA antagonist should block the facilitatory effects of prior noncontingent stimulation on subsequent acquisition of prefrontal cortex ICSS.

METHOD

Subjects and Procedure

Twenty-nine male Sprague-Dawley rats were implanted with 250 μ m monopolar electrodes aimed at the MFC while under sodium pentobarbital anesthesia (65.0 mg/kg, IP). After a one-week recovery period the rats were assigned to the following groups: Normal control (NC, N=9); Stimulation + saline (S + S, N=10); Stimulation + ketamine (S + K, N=10).

Rats from all 3 groups were placed in operant chambers for 20 min per day for 5 test days. The pretest chambers were identical to the chambers used for ICSS except that they lacked levers. The groups differed as follows: Group S + S received bursts of noncontingent, square wave pulses delivered to the MFC electrodes at the rate of $\frac{1}{4}$ s. The pulses were 400 μ A in amplitude, 0.1 ms wide and were delivered in 0.5-s trains at a rate of 100 Hz. The stimulation was administered 20 min per day for 5 days. Each day, immediately before being placed into the pretreatment chambers the rats were given IP injections of saline. Group S + K was treated identically except that rats received a 40.0 mg/kg dose of the NMDA antagonist ketamine prior to being placed in the pretreatment chambers.

Three days later the animals were tested for acquisition of ICSS in daily 30-min test sessions. The rats were placed into operant chambers and given 5 priming stimulations. The total number of responses per 30-min session were then recorded. The stimulation parameters were identical to those used in the pretreatment phase. The acquisition criterion was 15 responses/30 min session maintained for 3 consecutive test days. This criterion level is about twice the operant rate and has been found to re-

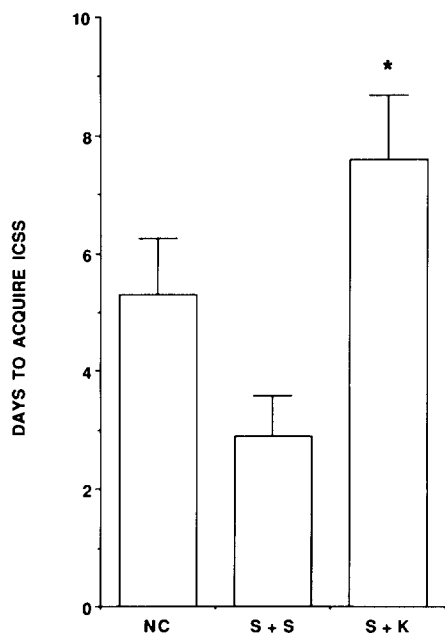


FIG. 1. Mean number of Days $\pm$ SEM to acquire ICSS for each of the three groups: normal controls (NC), saline + MFC stimulation group (S + S) and the ketamine + MFC stimulation group (S + K).

liably separate responders from nonresponders (7). Any animals that failed to meet this criterion within the 15-day test period were considered nonresponders and were discarded from the experiment.

Histology

At the conclusion of behavioural testing the animals were sacrificed with an overdose of sodium pentobarbital and perfused with 0.9% saline followed by 10% phosphate-buffered formalin. The brains were removed and stored in fixative prior to being sectioned at 40 μ m in a cryostat. Sections were subsequently stained with cresyl violet and electrode placements determined.

RESULTS

Three animals (Group S + S = 1, Group S + K = 2) did not acquire ICSS within the 15-day test period. In addition, 1 animal (Group S + S) was discarded due to loss of its electrode assembly.

From Fig. 1 it can be seen that Control animals acquired ICSS after 5.3 ± 3.13 days, Group S + S-treated animals acquired after 2.9 ± 2.18 days, while Group S + K acquired ICSS after 7.6 ± 3.24 days. Pretreatment with noncontingent stimulation resulted in more rapid acquisition of prefrontal ICSS: NC vs. S + S, Mann-Whitney $U(10,11) = 24.0$, $p < 0.05$. This facilitatory effect was blocked by ketamine: NC vs. S + K, $U(9,11) = 26.5$, n.s. All electrodes were found to be localized to the prelimbic area of the MFC (Fig. 2).

DISCUSSION

The present results suggest that the facilitatory effects of non-

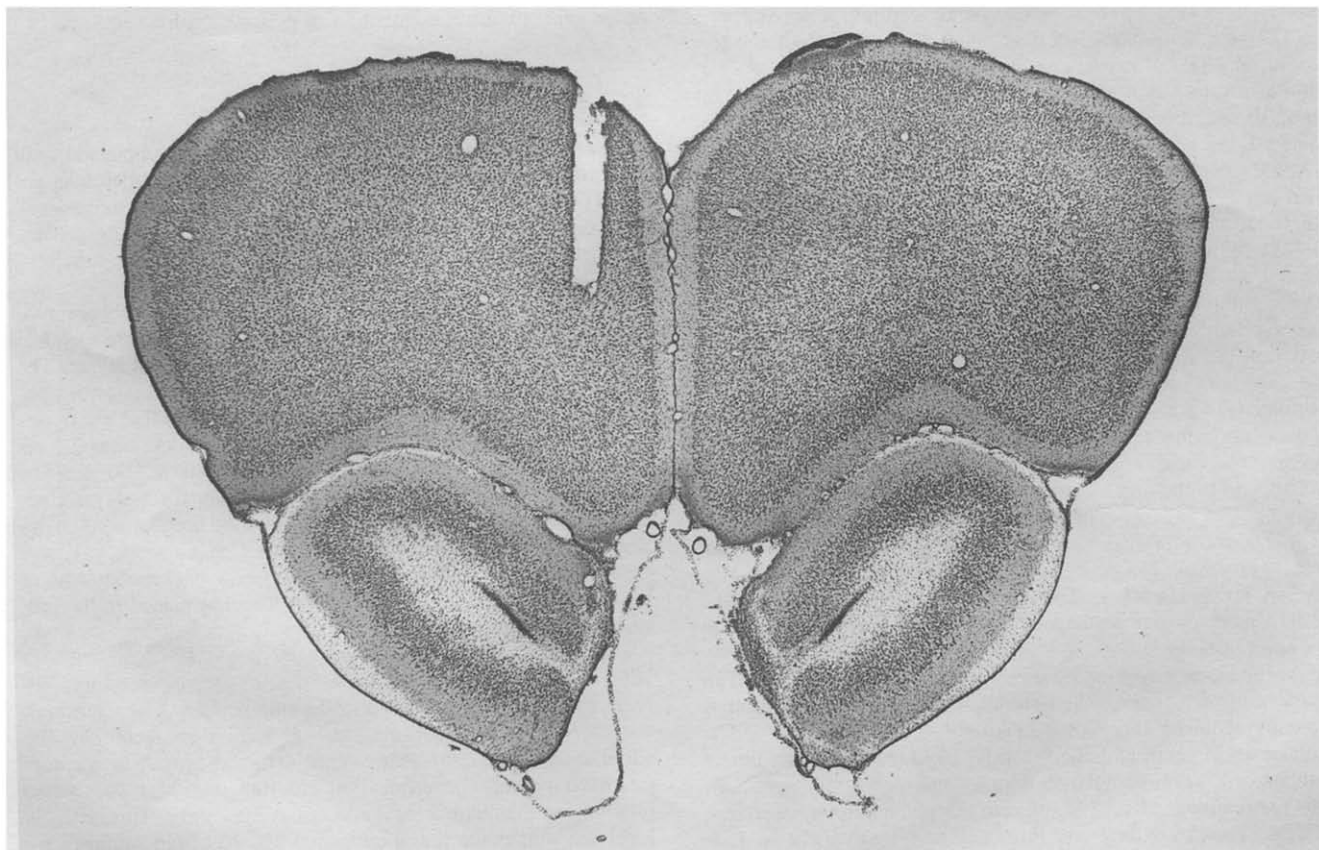


FIG. 2. A typical MFC electrode placement. Cresyl violet stain, 40 μ m section.

contingent MFC stimulation on subsequent acquisition of ICSS may involve the NMDA receptor. Consistent with this view are earlier findings showing that several of the efferent pathways implicated in MFC ICSS, such as cortico-cortical fibres (6, 23, 26), contain glutamate as their neurotransmitter (8). Also, NMDA antagonists such as MK-801 and AP5 have been shown to retard the development of kindling and LTP (4, 16, 19) and the prefrontal cortex has been found to support both of these phenomena (27,28). Indeed, given their many common characteristics it is possible that similar neural circuitry may underlie the development of ICSS, kindling and LTP. Robertson (24) has provided evidence for a more direct link between kindling and development of MFC ICSS by demonstrating that anticonvulsant agents such as diazepam or phenobarbital attenuate the facilitatory effects of noncontingent stimulation on acquisition of MFC ICSS. However, the parallels between kindling and MFC ICSS may be somewhat superficial since the frequency of the stimulation trains used to facilitate acquisition of MFC ICSS do not usually lead to behavioural seizures and may elevate seizure thresholds (22).

Another interpretation of these results is that ketamine blocked neuronal activity nonspecifically by way of its anesthetic properties. This seems unlikely since the dose of ketamine used (40 mg/kg) does not produce anesthesia (14) and many of its more nonselective effects (e.g., ataxia) undergo rapid tolerance, whereas

the ability to block kindling does not. Surprisingly, ketamine actually seemed to prolong MFC acquisition (7.6 days versus 5.3 for controls) in the present experiment. This result may be due to the use-dependent effects of noncompetitive antagonists such as ketamine, MK-801 and phencyclidine which block the NMDA-associated ion channel (13, 17, 31). In the absence of agonist, recovery from channel block has been found to be protracted (15,17). Thus, ketamine may have continued to partially block NMDA receptors into the first few ICSS sessions after drug treatment had ended. In support of this view are other data showing long-lasting behavioural impairments following a single injection of MK-801 (30).

Whatever the mechanism of ketamine's effects on MFC ICSS, the above results provide additional support for the view that the NMDA receptor underlies quite diverse forms of neural plasticity. Further, like LTP and kindling, MFC ICSS may provide a useful model with which to investigate the neurochemical basis of learning and memory.

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REFERENCES

1. Benvenia, M. K.; Spaulding, T. C. Amnesic effect of the novel anticonvulsant MK-801. *Pharmacol. Biochem. Behav.* 30:205-207; 1988.
2. Cain, D. P.; Desborough, K. A.; McKittrick, D. J. Retardation of amygdala kindling by antagonism of NMDA-aspartate and muscarinic cholinergic receptors: Evidence for the summation of excitatory mechanisms in kindling. *Exp. Neurol.* 100:179-187; 1988.
3. Cain, D. P. Long-term potentiation and kindling: how similar are the mechanisms? *Trends Neurosci.* 12:6-10; 1989.
4. Collingridge, G. L.; Bliss, T. V. P. NMDA receptors—their role in long-term potentiation. *Trends Neurosci.* 10:288-293; 1987.
5. Corbett, D.; Laferrière, A.; Milner, P. M. Plasticity of the medial prefrontal cortex: Facilitated acquisition of intracranial self-stimulation by pretraining stimulation. *Physiol. Behav.* 28:531-534; 1982.
6. Corbett, D.; Laferrière, A.; Milner, P. M. Elimination of medial prefrontal cortex self-stimulation following transection of efferents to the sulcal cortex in the rat. *Physiol. Behav.* 29:425-431; 1982.
7. Corbett, D.; Silva, L. R.; Stellar, J. R. An investigation of the factors affecting development of frontal cortex self-stimulation. *Physiol. Behav.* 34:89-95; 1985.
8. Cotman, C. W.; Monaghan, D. T.; Otterson, O. P.; Storm-Mathisen, J. Anatomical organization of excitatory amino acid receptors and their pathways. *Trends Neurosci.* 10:273-280; 1987.
9. Errington, M. L.; Lynch, M. A.; Bliss, T. V. P. Long-term potentiation in the dentate gyrus: Induction and increased glutamate release are blocked by D (-)-aminophosphonovalerate. *Neuroscience* 20: 279-284; 1987.
10. Feeser, H. R.; Kadis, J. K.; Prince, D. A. Dextromethorphan, a common antitussive, reduces kindled amygdala seizures in the rat. *Neurosci. Lett.* 86:340-345; 1988.
11. Kleinschmidt, A.; Bear, M. F.; Singer, W. Blockade of NMDA receptors disrupts experience-dependent plasticity of kitten striate cortex. *Science* 238:355-358; 1987.
12. Heale, V.; Harley, C. MK-801 and AP5 impair acquisition, but not retention, of the Morris milk maze. *Pharmacol. Biochem. Behav.* 36:145-149; 1990.
13. Kemp, J. A.; Foster, A. C.; Wong, E. H. F. Non-competitive antagonists of excitatory amino acid receptors. *Trends Neurosci.* 10:294-298; 1987.
14. Leccese, A. P.; Marquis, K. L.; Mattia, A.; Moreton, J. E. The anticonvulsant and behavioral effects of phencyclidine and ketamine following chronic treatment in rats. *Behav. Brain Res.* 22:257-264; 1986.
15. Lodge, D.; Johnson, K. M. Non-competitive excitatory amino acid receptor antagonists. *Trends Pharmacol. Sci.* 11:81-86; 1990.
16. McNamara, J. O.; Russell, R. D.; Rigsbee, L.; Bonhaus, D. W. Anticonvulsant and antiepileptic actions of MK-801 in the kindling and electroshock models. *Neuropharmacology* 27:563-568; 1988.
17. MacDonald, J. F.; Miljkovic, Z.; Pennefather, P. Use-dependent block of excitatory amino-acid currents in cultured neurons by ketamine. *J. Neurophysiol.* 58:251-265; 1987.
18. Mintz, M. I.; Rose, C.; Herberg, L. J. The effect of the NMDA receptor antagonist, MK-801, on the course and outcome of kindling. *Pharmacol. Biochem. Behav.* 35:815-821; 1990.
19. Morris, R. G. M.; Anderson, E.; Lynch, G. S.; Baudry, M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate antagonist, AP5. *Nature* 319:774-776; 1986.
20. Morris, R. G. M.; Halliwell, R. F.; Bowery, N. Synaptic plasticity and learning II: Do different kinds of plasticity underlie different kinds of learning? *Neuropsychologia* 27:41-59; 1989.
21. Nicoll, R. A.; Kauer, J. A.; Malenka, R. C. The current excitement in long-term potentiation. *Neuron* 1:97-103; 1988.
22. Racine, R. J.; Burnham, W. M.; Gartner, J. G.; Levitan, D. Rates of motor seizure development in rats subjected to electrical brain stimulation: Strain and inter-stimulation interval effects. *Electroencephalogr. Clin. Neurophysiol.* 35:553-556; 1973.
23. Robertson, A.; Laferrière, A.; Milner, P. M. Development of brain stimulation reward in the medial prefrontal cortex: Facilitation by prior electrical stimulation of the sulcal prefrontal cortex. *Physiol. Behav.* 28:869-872; 1982.
24. Robertson, A.; Laferrière, A.; Milner, P. M. Treatment with anticonvulsant drugs retards the development of brain-stimulation reward in the prefrontal cortex. *Physiol. Behav.* 29:275-280; 1982.
25. Robinson, G. S.; Crooks, G. B.; Shinkman, P. G.; Gallagher, M. Behavioral effects of MK-801 mimic deficits associated with hippocampal damage. *Psychobiology* 17:156-164; 1989.
26. Routtenberg, A.; Sloan, M. Self-stimulation in the frontal cortex of *Rattus norvegicus*. *Behav. Biol.* 7:567-572; 1972.
27. Seidel, W. T.; Corcoran, M. E. Relations between amygdaloid and anterior neocortical kindling. *Brain Res.* 385:375-378; 1986.
28. Sutor, B.; Hablitz, J. J. Long-term potentiation in frontal cortex: role of NMDA-modulated polysynaptic excitatory pathways. *Neurosci. Lett.* 97:111-117; 1989.
29. Ward, L.; Mason, S. E.; Abraham, W. C. Effects of the NMDA antagonists CPP and MK-801 on radial arm maze performance in rats. *Pharmacol. Biochem. Behav.* 35:785-790; 1990.

30. Wishaw, I. Q.; Auer, R. A. Immediate and long-lasting effects of MK-801 on motor activity, spatial navigation in a swimming pool and EEG in the rat. *Psychopharmacology (Berlin)* 98:500–507; 1989.
31. Wong, E. H. F.; Kemp, J. A.; Priestley, T.; Knight, A. R.; Woodruff, G. N.; Iverson, L. L. The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. *Proc. Natl. Acad. Sci. USA* 83: 7104–7108; 1986.