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Phencyclidine Raises Kindled Seizure Thresholds

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FREEMAN, F. G., M. F. JARVIS AND P. DUNCAN. *Phencyclidine raises kindled seizure thresholds*. PHARMAC. BIOCHEM. AND BEHAV. 16(6) 1009–1011, 1982.—Phencyclidine (PCP) has been reported to have both anesthetic and seizure-inducing properties. In the present experiment the effect of PCP on previously established seizures, kindled in the amygdala, was examined, using rats as subjects. In a repeated measures design three doses of PCP (1, 2 and 5 mg/kg) were compared with a saline control condition. The high dose of PCP was found to significantly increase seizural afterdischarge thresholds, while not affecting seizure durations.

Phencyclidine Kindling Thresholds Amygdala

PHENCYCLIDINE (PCP), though introduced as an anesthetic, has been characterized as also having excitant and convulsant properties [7]. Excitatory and convulsant behaviors have been reported primarily in rodents although overdoses by humans are reported to produce convulsions. At subconvulsive doses PCP produces stimulant effects similar to those of amphetamine [1]. In mice, for example, low doses (2–4 mg/kg) produce increased movement, higher doses produce ataxia, and very high doses (20 mg/kg) can induce convulsions.

Ketamine, a derivative of PCP, has basically the same behavioral effects as PCP. The only differences are that it is slightly less likely to produce psychiatric side effects, produces shorter duration catalepsy, and is less potent in producing grand mal seizures. Ketamine also can produce seizures in the limbic system, especially the amygdala and hippocampus. Because of the similarities between ketamine and PCP, and because PCP is more potent in eliciting seizures, PCP might be expected to potentiate seizures elicited by electrical stimulation of the brain and to lower seizure thresholds. However, there is some evidence [2] that seizure thresholds are increased by PCP, when the seizures are elicited by inhalation of flurothyl.

The purpose of the present experiment was to examine the effects of PCP on afterdischarge (AD) and motor-seizure (MS) thresholds kindled in the amygdala. Kindling is an experimental model of epilepsy in which animals receive low-intensity electrical brain stimulation once per day until a full clonic convulsion is elicited. The amygdala is the area of the brain most easily kindled [3].

METHOD

Subjects were 9 Long Evans hooded rats weighing from 350–400 g. All subjects had undergone kindling procedures and had experienced approximately 23 motor seizures (MS) prior to the onset of this experiment. These seizures were elicited in the conduction of an experiment investigating the effects of pairing a tone with the kindling stimulus (unpublished data). The long-term effects on brain functioning resulting from that experiment were apparently minimal and were assumed not to intereact with the effects of PCP.

Apparatus

EEG recordings were made with a Grass model 7p511g EEG amplifier and 7dwu8p oscillograph. For brain stimulation a Grass model S48 stimulator was used in conjunction with a Grass model PSIU 6B photoelectric stimulus isolation unit which had a constant current output. All EEG recordings were made in a 55 by 30 by 30 cm chamber.

Drugs

Phencyclidine hydrochloride, obtained from National Institute of Drug Abuse, was dissolved in normal saline solution at a concentration of 2 mg per ml.

Surgery

All animals were anesthetized with an intraperitoneal (IP) injection of 50 mg/kg sodium pentobarbital (Nembutal). The animals were placed in a stereotaxic instrument, a midline incision was made on the scalp and the skin and muscle were retracted. A bipolar electrode made of twisted platinum iridium wire insulated with Teflon was implanted unilaterally, on the left side in half the animals and on the right side in the others, into the amygdala. With the skull tilted (incisor bar 5.0 mm above the IA axis) and using bregma as the zero point, the following coordinates were used, according to the atlas of Pellegrino and Cushman [5]: posterior, 0.8 mm, lat-

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TABLE 1

MEAN EFFECT OF PCP ON AFTERDISCHARGE (AD) AND MOTOR SEIZURE (MS) THRESHOLDS AND DURATIONS

	PCP Dose (mg/kg)			
	Saline Control	1	2	5
AD threshold in μA (SEM)	41.9 (6.1)	53.2 (11.6)	56.5 (10.7)	96.4 (29.9)
MS threshold	41.9 (6.1)	65.5 (12.6)	102.7 (44.1)	102.1 (30.0)
AD duration in seconds (SEM)	79.9 (5.3)	53.2 (15.0)	67.4 (13.0)	67.4 (13.9)
MS duration	79.9 (5.3)	73.2 (13.1)	73.6 (12.9)	81.6 (5.9)

eral, + or −4.5 mm, ventral 8.0 mm. Four 0–80 stainless steel anchor screws were placed in the skull. Amphenol pins were crimped onto the end of the electrode and placed in a connector strip which was cemented, with dental acrylic, to the skull surface. The wound was sutured closed and the animals were returned to their home cage for a one-week recovery period.

Procedure

One week after surgery the kindling procedure was initiated. The EEG of the amygdala was recorded from each animal for approximately 30 sec. Animals were then disconnected from the EEG machine and connected to the stimulator via a rotary switch. A 1 sec train of square wave pulses, 50 pps, 1.0 msec duration, 400 μa, was then delivered to the animal. The animal was then reconnected to the EEG machine to determine the presence of AD's. The animal's behavior was also rated by the experimenter on a scale of 1–5 similar to that used by Racine [6] with a 5 indicating the occurrence of clonic convulsions.

Following the elicitation of approximately 22 stage 5 seizures, as previously described, threshold testing began. Seizure thresholds were assessed using an ascending method of limits. Subjects were stimulated every minute according to the following stimulus schedule until a stage 5 seizure was produced: 20 μA, 24, 30, 36, 42, 50, 60, 75, 90, 110, 130, 160, 200, 240, 280, 330, 400. The current level which elicited a seizure was designated as the threshold. On the first day of threshold testing, all subjects were given a 0.3 cc intraperitoneal (IP) injection of saline solution 15 minutes before threshold testing. Successive threshold tests were performed once every 48 hours. For each of these tests the subjects were injected IP with either 1, 2 or 5 mg/kg of phencyclidine 15 minutes prior to being tested. The order of doses administered was counterbalanced across all subjects. After the injection, EEG recordings of 20-sec duration were taken at five minute intervals prior to the onset of threshold testing.

At the completion of the experiment all subjects were anesthetized with an overdose of sodium pentobarbital and perfused intracardially with 0.9% saline solution followed by 10% Formalin in saline solution. The brains were removed and stored in 10% Formalin for at least two days. Frozen sections 80 μm thick through the electrode track were mounted on slides and stained with thionin.

RESULTS AND DISCUSSION

Histological examination indicated that all subjects had electrode placements in the amygdala; four were in the basolateral nucleus, two in the lateral, one in the medial, and one in the anterior amygdaloid nucleus. One subject lost its electrode prior to completion of the experiment, so histological verification of the electrode site was not obtained.

The results of the experiment are presented in Table 1. PCP produced a dose-related increase in kindled AD thresholds. A repeated measures analysis of variance performed on the AD thresholds revealed a statistically significant, $F(3,21)=4.05$, $p<0.025$, effect of PCP dosage. Further analysis via Newman-Keuls comparisons showed that the high dose (5 mg/kg) of PCP produced significantly higher thresholds than the two lower doses and the saline control ($p<0.05$). No other differences were significant. As seen in Table 1, the motor seizure thresholds also increased with increasing doses of PCP. However, due to a high degree of variability, these differences were not statistically significant. Nevertheless, the differences were in the same direction as the AD thresholds and directly opposite of what would be expected based on previous reports of increased seizure susceptibility and on Winter's [7] characterization of the effect of PCP. The results, however, do confirm the report of Geller *et al.* [2] that PCP raises seizure thresholds elicited by flurothyl.

As seen in Table 1, the AD durations appeared to be longer for the control group than for the PCP injected groups. The MS durations appear to be fairly constant across all conditions. None of these conditions, however, were significantly different from one another.

The mechanism by which PCP raised thresholds is not clear. Possibly, localized AD's were elicited by the PCP injections prior to threshold testing. It has been shown that the elicitation of an AD will have an inhibitory effect on subsequently elicited AD's and MS's [4]. Conceivably, PCP-elicited AD's caused the kindled threshold to increase. However, in the sample EEG records taken every five minutes between the injection and the threshold test there was no evidence of any ADs or spike activity. Perhaps a larger sample of EEG following the PCP injection might reveal some anomalous activity. However, other behavioral indices of seizure activity (e.g., mouth twitching, forelimb clonus, etc.) were not observed.

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