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EFFECTS OF PHENCYCLIDINE, LSD AND AMPHETAMINE ON NEURONAL ACTIVITY IN THE POSTERIOR PARIETAL ASSOCIATION CORTEX OF THE MONKEY

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Summary—The effects of three drugs of abuse, phencyclidine, LSD and amphetamine on the multineuronal impulse activity of the posterior parietal association cortex was studied in non-anaesthetized stump-tailed (*Macaca speciosa*) monkeys. Moderate doses of phencyclidine (less than 0.5 mg/kg) produced a rhythmic discharge and increased the spontaneous activity and the responses to visual, somaesthetic and auditory stimuli. The increase in activity was very marked in comparison with the effects of alcohol and pentobarbital which usually merely decreased the activity in this region. Larger doses of phencyclidine depressed both the spontaneous activity and sensory responses. Similar effects on the spontaneous activity were noted at recording sites where cellular responses were related to motor behaviour. Amphetamine and LSD produced only minor effects. Phencyclidine thus has a unique effect in the parietal association cortex. Small doses of phencyclidine which produce euphoria and hallucinations caused a strong increase in neural activity and larger doses, that produce anaesthesia, blocked the activity.

Phencyclidine was originally developed as a veterinary tranquillizer (Domino, 1964) but it is nowadays also abused in the streets under the names PCP or "angel dust" (Liden, Lovejoy and Costello, 1975; Lemberger and Rubin, 1976). Its congener ketamine is used in human surgery for anaesthesia in minor operations. These drugs have been called "dissociative anaesthetics" and are thought to block the sensory inflow to the association systems of the brain (Domino, 1964; Domino, Chodoff and Corssen, 1965). During induction of ketamine anaesthesia the recipient is said to feel dissociated from his environment including his own extremities (Goodman and Gilman, 1970, p. 97). On the other hand it has also been shown that ketamine produces seizure activity in the neocortex and in the hippocampus of the cat (Kayama and Iwama, 1972), and thus it could be considered epileptogenic (Winters, 1972).

The effects of phencyclidine on cellular activity was investigated with microelectrode recording techniques in the parietal associative cortex of non-anaesthetized monkeys in which the behavioural actions of the drug could be observed simultaneously. For comparison, the effects of the other two drugs of abuse, amphetamine and LSD were also studied and the results were compared with those produced by alcohol and pentobarbital in the same cortical region. It was found that the neuronal effects of phencyclidine were much stronger and quite different in character from those of the other drugs tested.

METHODS

Four non-anaesthetized, stump-tailed monkeys were used in these experiments. Recordings of neural activity were performed using glass-covered tungsten microelectrodes made with a modification of the method described by Levick (1972). The electrodes were introduced into the brain with a hydraulic micromanipulator through the intact dura mater using a modification of the Evarts' technique of recording from non-anaesthetized animals (Evarts, 1968) as described earlier (Hyvärinen and Poranen, 1974; Hyvärinen, Laakso, Roine, Leinonen and Sippel, 1978). The drug experiments lasted for up to several hours, and it was not possible to hold single units in non-anaesthetized, moving animals all this time. Multineuronal impulse activity was therefore recorded with electrodes exposed about 100 μ at the tip. The multineuronal activity was filtered at 300, 500 or 1000 Hz to eliminate slow waves from the responses, and rectified and integrated using the apparatus described by Weber and Buchwald (1965). High-pass filtering completely eliminated slow wave signals from the recording leaving only action potential spikes which, judged from variability in their amplitudes, were derived from approximately five to ten neurons (Fig. 1). Because the absolute levels of the responses depended on the electrode used, the site of recording and the time constant selected for integration, the results were expressed as a percentage of the response amplitudes in the control responses (% control) or in the largest responses (% maximum) (Fig. 1).

The recording region in the lateral part of the posterior parietal association cortex (Brodmann's area 7 or von Bonin and Bailey's area PF) was the same as in a previous study (Hyvärinen *et al.*, 1978). The recording region was determined using stereotaxic coordinates and by mapping the location of the adja-

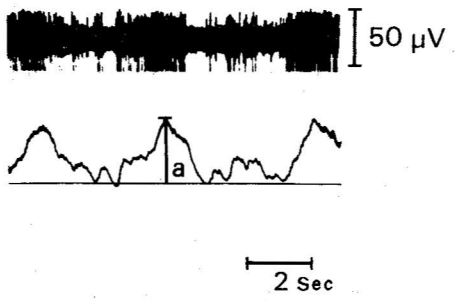

Fig. 1. Multineuronal impulse activity recorded with a coarse microelectrode (upper trace) and the same activity rectified and integrated (lower trace). Three neuronal control responses to reaching with the ipsilateral hand are seen in the figure. Measurement of the amplitude (a) of an integrated response is shown. Amplitudes of ten consecutive integrated responses were measured and their means and standard deviations were calculated. The mean and standard deviation values obtained during the action of the drugs was then expressed as percentage of the mean of the control amplitude or of the maximum amplitude obtained during the experiment.

cent primary somatosensory cortex with coarse microelectrodes. In three of the four monkeys (four hemispheres) the recording region was anatomically verified after the experiments when the animals were killed and their brains investigated. One of the monkeys is still alive and in this monkey the location of the recording area (one hemisphere) was based entirely on anatomical measurements and functional criteria.

The behavioural actions of the drugs were monitored simultaneously with the neuronal recordings by observing the overall behaviour of the monkey and by testing its ability to reach for food rewards. For a quantitative indication of the drug effect, the monkey's accuracy in reaching for food rewards was estimated by the experimenters using an arbitrary scoring system. Ten points were given for normal rapid and accurate grasping of food from the experimenter's hand, zero points for no attempt to reach and intermediate values for intermediate accuracies and speeds. Three observers were used for the scoring and obtained results which did not differ from each other by more than $\pm 10\%$. Eye movements were observed by recording electro-oculograms with four Ag-AgCl electrodes implanted around the orbits (Bond and Ho, 1970).

The drugs used were phencyclidine hydrochloride (Sernylan®) from Parke-Davis & Co, Pontypool, Gwent, U.K., *d*-amphetamine from E. Merck, Darmstadt and lysergic acid diethylamide (LSD-25) from Sandoz Ltd, Basle. Phencyclidine diluted with physiological saline to contain 10 mg/ml was given intramuscularly or intravenously. Amphetamine was given in a solution of 20 mg/ml 1 to 2 mg subcutaneously. A solution of 10 μg/ml of LSD-25 was injected intravenously, 10 to 20 μg/kg divided in 1 to 5 doses. Sixteen experiments were performed using phencyclidine, six using amphetamine and four using LSD.

RESULTS

Phencyclidine

The neuronal activity was triggered by sensory stimuli at eight of the 16 recording sites where the effects of phencyclidine were studied. These recording sites responded to cutaneous stimulation (3 sites), vis-

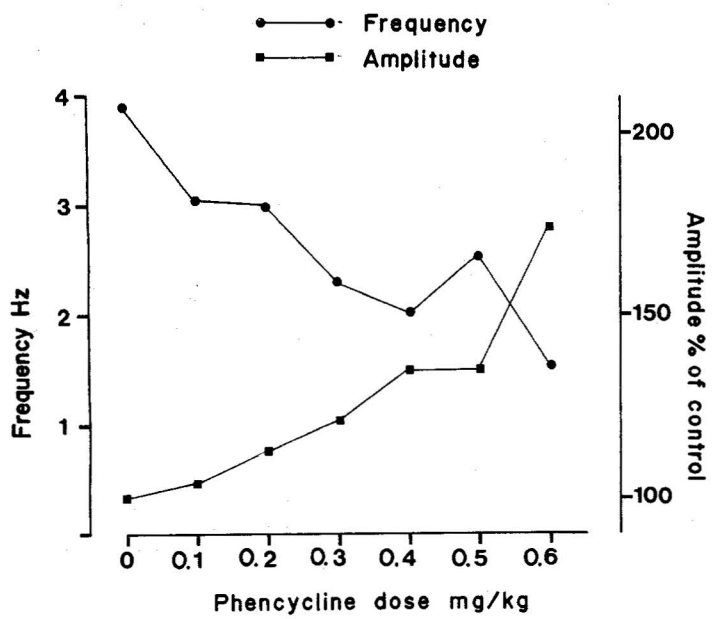

Fig. 2. The effect of phencyclidine on the amplitude of spontaneous activity and on the frequency of its rhythm. The frequency was determined by counting the number of waves in the integrated record per time unit. Means of 10 consecutive determinations.

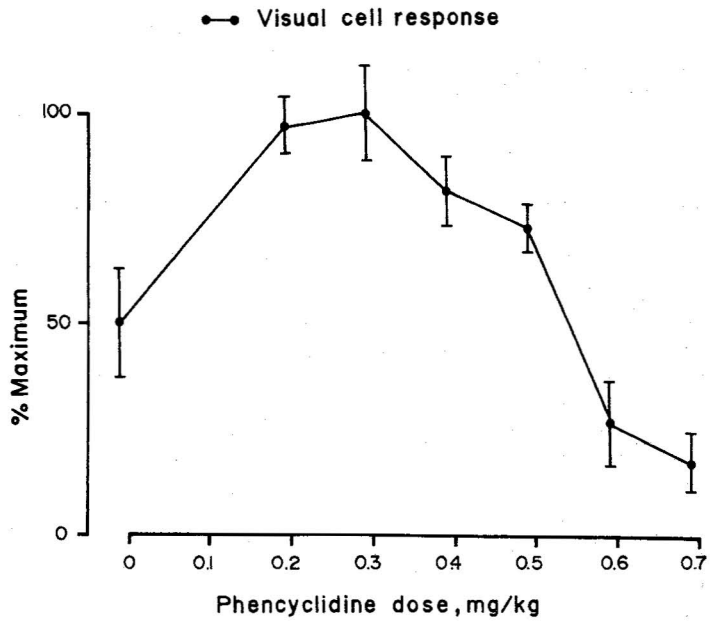

Fig. 3. Effect of phencyclidine on the amplitudes of integrated responses to visual stimuli at a locus in area 7 responsive to approach of objects toward the face of the monkey. Mean and standard deviation values of 10 responses.

ual stimulation (3 sites), or auditory stimulation (2 sites). Neuronal activity at two recording sites was related to motor behaviour of the monkey (reaching, grasping), and at 6 sites both sensory stimuli and motor behaviour activated the cells. The spontaneous activity was similarly affected at all types of recording sites. The neuronal responses were studied using sensory stimuli, because these responses could also be investigated when the monkey ceased to perform motor acts during the action of the drug. The effects of phencyclidine on the responses of different cell groups were of the same kind although variable in magnitude.

With small doses (less than 0.5 mg/kg) phencycli-

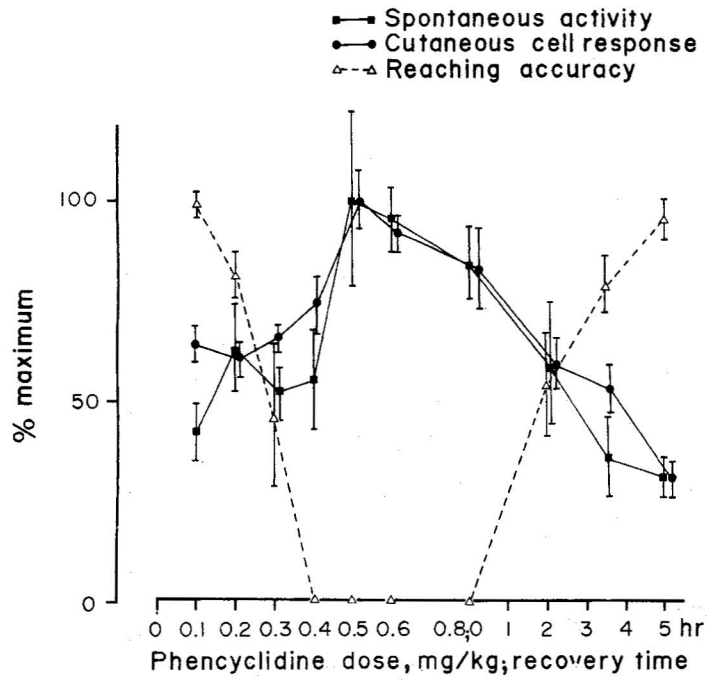

Fig. 4. The effect of increasing dose and recovery time on cutaneous responses, spontaneous activity and reaching accuracy at a locus in area 7 responsive to cutaneous stimulation of the left leg and the pelvic region.

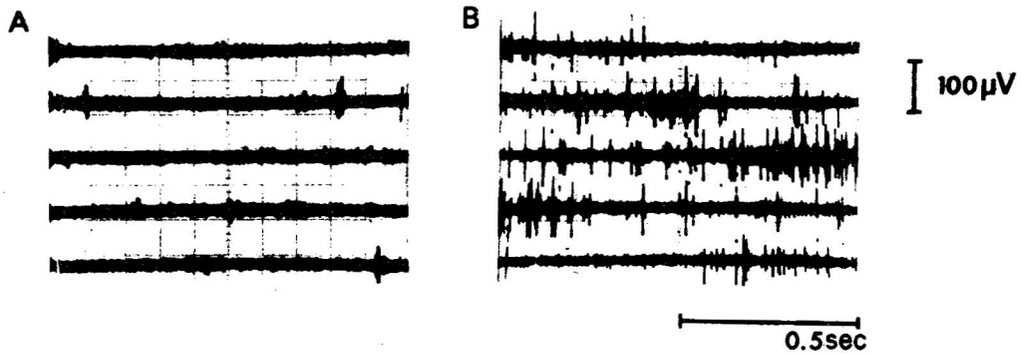

Fig. 5. Effect of LSD on the spontaneous multineuronal impulse activity recorded at a locus in area 7 where the activity was triggered by large stimuli moving from left to right in the visual field. Activity was not associated with eye movements. A—spontaneous activity recorded prior to the injection of the drug. B—Spontaneous activity 40 min after an intravenous injection of 10 μg/kg of LSD. Both recordings were made keeping the monkey's eye-lids closed. The recordings are continuous.

dine produced symptoms typical of this drug including deterioration of motor control, wandering gaze, mastication and increased salivation. In this phase the spontaneous activity started to become rhythmic and its amplitude increased (Fig. 2) in all experiments. At the same time the amplitudes of the integrated responses to sensory stimuli increased (Figs 3 and 4). With larger doses the animals stopped reacting to external stimuli, including pain and stopped reaching for food rewards. Spontaneous muscular contractions that were often synchronous with the bursts of spontaneous activity appeared at this phase of the experiment. The frequency of the rhythmic discharge in the spontaneous activity also decreased with increasing dose of the drug (Fig. 2). With increasing dose level, the amplitudes of the responses to sensory stimuli started to decline (Figs 3 and 4). At a dose of approximately 1 mg/kg they were considerably less than in the control recordings. At still higher doses there were periods of complete lack of activity at the recording sites.

LSD

Because LSD is known to produce visual hallucinations (Goodman and Gilman, 1970, p. 297), recording sites activated by visual stimuli were selected for the study of LSD. Two of the four sites where LSD was studied were activated by visual stimuli moving in the visual field in a specific direction, and two were activated by visual presentation of food that the monkey was interested in. No definite connection between the neuronal activity and eye movements was noted at these sites.

In one experiment a strong increase in the spontaneous neuronal activity was recorded in response to injection of LSD. Prior to the injection only moving visual stimuli could activate the recording site, and closing of the eyes stopped the activity completely. However, ten minutes after the injection of LSD the monkey became sleepy, spending much of the time with the eyes closed. Frequent eye movements were noted behind the lids. These symptoms lasted for about one hour. During this period intense spontaneous activity was recorded, and it was not diminished by closure of the eyes (Fig. 5). However, no changes were observed in the visual responses elicited by moving visual stimuli. In the other three experiments performed with another monkey no effects of LSD were discernible on the monkey's behaviour, the spontaneous cellular activity or on the responses to stimuli.

Amphetamine

The effects of amphetamine were studied in six experiments all performed on one monkey. The recording sites in these experiments in the lateral part of area 7 were activated by somaestetic stimuli (cutaneous stimulation or stimulation of muscles). At four sites visual mechanisms were also represented and activity at one site was also triggered by reaching movements.

Within one to two minutes after a subcutaneous injection of amphetamine the animal stopped reaching for food rewards. Shortly afterwards a decrease in the heart rate was observed and in 20 to 30 min stereotyped movements appeared which lasted for several hours (Randrup and Munkvad, 1967). After the injection, a small reduction in responses (Fig. 6) or no effect at all was noted in the cellular activity. The effects of amphetamine were also minor in comparison with effects produced by alcohol and pentobarbital shown for comparison in Figure 6 and reported separately (Hyvärinen *et al.*, 1978; Hyvärinen *et al.*, unpublished).

DISCUSSION

These results indicate that phencyclidine strongly influences the neuronal activity in the posterior parietal association cortex. Two phases could be discerned in this effect. Low doses, that are known to produce euphoria, hallucinations and thought disorders (Domino, 1964; Lemberger and Rubin, 1976), increased the spontaneous activity as well as the re-

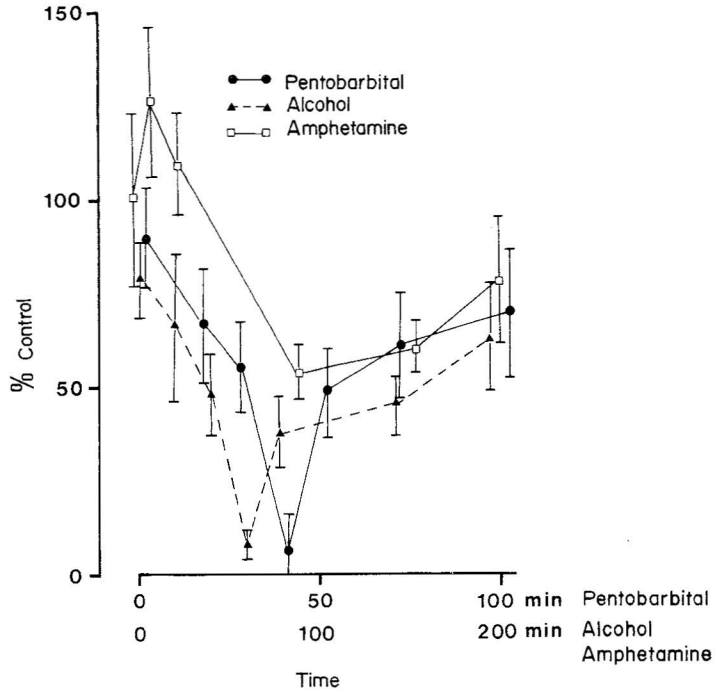

Fig. 6. Effects of pentobarbital, alcohol and amphetamine on visual responses at a site responsive to approaching visual stimuli. An intravenous infusion of 16 mg/kg of pentobarbital was given during 35 min after the control record. In another experiment one day later 2.8 g/kg of alcohol was given during 50 min after the control record. Three days later a recording with amphetamine was done at the same site giving 2 mg/kg of *d*-amphetamine in one subcutaneous injection immediately after the control record.

sponses to sensory stimuli. Large doses, however, had a depressant effect on neuronal activity. This drug also produced a strong rhythmicity in the neuronal activity that at higher doses was often synchronous with muscular contractions. On the basis of these data it is proposed that, phencyclidine at sufficient dosage, blocks sensory inflow in the parietal association cortex. This finding lends support to the notion that it acts as a "dissociative" anaesthetic. However, at moderate dosage it also produces strong, rhythmic spontaneous activity, and it could thus be considered "epileptogenic" as has been claimed for its congener ketamine (Kayama and Iwama, 1972; Winters, 1972).

It has previously been shown by Roppolo, Werner, Whitsel, Dreyer and Petrucelli (1973) that phencyclidine affects the secondary somatosensory cortex of the monkey in doses comparable to those that produced an increased activity in this study and that the effect of this drug at this dose is less on the primary somatosensory cortex. Kayama and Iwama (1972) have shown that ketamine affects the neocortex and the hippocampus of cats. Thus, the actions of these drugs are probably widespread in the brain and not limited in the posterior parietal association cortex. However, at this site the effects of phencyclidine are quite distinct. In comparison with the predominantly suppressing effects of alcohol (Hyvärinen *et al.*, 1978) and pentobarbital (Hyvärinen *et al.*, unpublished) on the neuronal activity in this region, the facilitation of activity by phencyclidine at moderate dosage is remarkable. It is also contrasted with the small and inconsistent effects of amphetamine and LSD in this region.

In one experiment LSD produced a strong increase in the spontaneous activity recorded at a site responsive to moving visual stimuli, and this activity was not diminished by closing of the eyes. The increased spontaneous activity may have been correlated with hallucinatory dreaming activity. No changes in the visual responses was noted, however. Therefore, the effects produced by LSD in this part of the cortex are clearly less distinct than those produced by phencyclidine.

The effects of amphetamine were small in comparison with phencyclidine and also in comparison with pentobarbital and alcohol. The psychological stimulatory effects of amphetamine were not reflected in changes in cellular activity; no change was noted in cellular activity, or it was decreased. Because the monkey became totally uninterested in food rewards within a few minutes after the injection of amphetamine, the possible effects of this drug on the neuronal responses to reaching could not be reliably tested. The lack of interest in food is a well known effect of amphetamine and this effect is probably produced by stimulation of the hypothalamic satiety system (Goodman and Gilman, 1970, p. 503). The lack of the motivational drive may then be reflected secon-

darily in the parietal cortex where cells related to purposeful reaching do not discharge.

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