

8. THE EFFECT OF CHLORPROMAZINE ON THE AFFERENT PATHWAYS OF THE HIPPOCAMPUS

Hiroshi TAKAGI, M.D. AND Takashi BAN, M.D.

Department of Pharmacology Faculty of Medicine, Kyoto University, Kyoto

Recent anatomical, physiological and clinical investigations have led to interest in the role of the limbic system for emotional behavior. Hippocampal and amygdaloid connections have been determined by Green and Adey¹⁾ and Gloor²⁾ using the electrophysiological methods.

In our laboratory, Takagi et al.³⁾ have reported the effect of psychotropic drugs on the several afferent pathways of the central nervous system of the cat.

The experiments reported here were undertaken in an attempt to clarify the mode of action of chlorpromazine on the limbic system, especially on the afferent and efferent pathways of the hippocampus.

Methods

The experiments were carried out on 24 cats of both sexes. Surgical procedures were performed under ether anesthesia, then the spinal cord was transected at the C₁ level (encéphale isolé) and maintained in a stereotaxic apparatus after which artificial respiration was instituted and anesthetic discontinued. About 2 hours had elapsed before experimental data were recorded. Cortical recordings were taken from monopolar silver wire usually placed epidurally. Subcortical recordings were made from bipolar electrodes with 1 mm separation in vertical dimension. Square wave stimuli were given from a stimulator with an isolation unit. Recordings were made on an 2-channel electroencephalograph and a cathode-ray oscillograph in connection with R-C coupled amplifier. All drugs were administered by the intravenous route.

Results

Effect on hippocampal seizures induced by stimulation of fornix: Drug effects on the duration and threshold of hippocampal seizures produced by repetitive stimulation of the precommissural fornix were investigated. Trains of stimuli at 150/sec. for 5 sec. were applied at gradually increasing voltages until seizures initiated. The duration and threshold of seizures varies on each animal. When the strength of the stimulus was sufficient, these seizure discharges spread to other

This study was supported in part by a Grant in Aid for Scientific Research from the Ministry of Education.

limbic structures and cerebral cortices and ended simultaneously. In doses of 1 to 3 mg/kg chlorpromazine caused a reduction in duration and an elevation in threshold of seizures. In cases received 3 mg/kg chlorpromazine the seizures were completely suppressed and recovery gradually became apparent about an hour after administration of drug (Fig. 1).

Hexobarbital sodium in doses of 10 to 20 mg/kg caused a marked reduction in duration and an elevation in threshold.

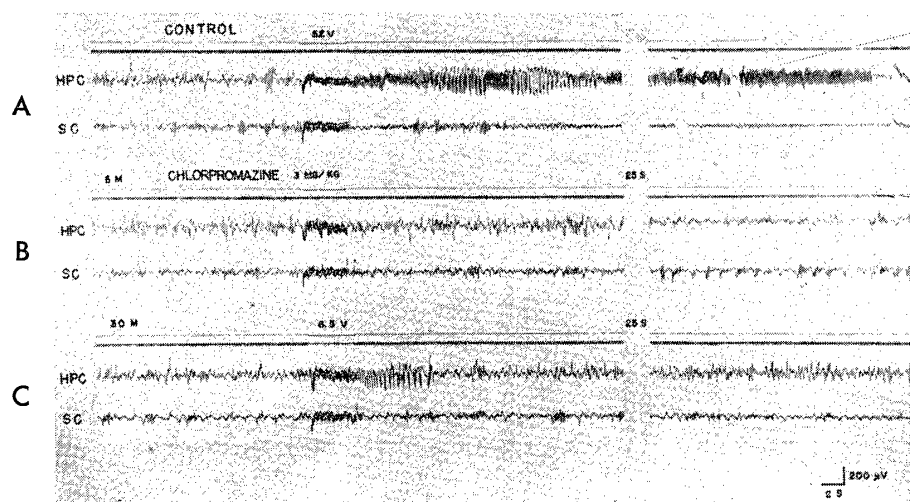


Fig. 1. Effect of chlorpromazine on the hippocampal seizures produced by stimulation of the fornix at 150/sec. Recordings were taken from hippocampus (HPC) and sensory cortex (SC).

A group: control (stimulated at 5.2V)

B group: 5 min. after 3mg/kg chlorpromazine (stimulated at 5.2V)

C group: 30min. after injection (stimulation was increased to 6.5V)

Calibration: ordinate 200 μ V, abscissa 2 sec.

Effects on afferent pathways to hippocampus:

1) Afferent from fornix to hippocampus: It has been reported by Green and Adey¹⁾ that a single shock to the fornix evoked a potential in the hippocampus and repetitive stimuli (10/sec) to the fornix caused a potentiation of the evoked potential, namely post-tetanic potentiation (PTP) which was also confirmed by the authors.

Chlorpromazine, at 1 to 5 mg/kg caused no significant changes in the single shock potential as well as in PTP (Fig. 2).

Hexobarbital sodium in dose of 10 mg/kg blocked a development of potentiation without affecting on single evoked potential.

2) Afferent from amygdala to hippocampus: Gloor²⁾ has reported that a single shock to the basolateral nuclei of amygdala produced a evoked potential in the hippocampus and its potentiation or recruitment was observed after repetitive stimuli to the same site of amygdala. In the present experiment, potentiations were more

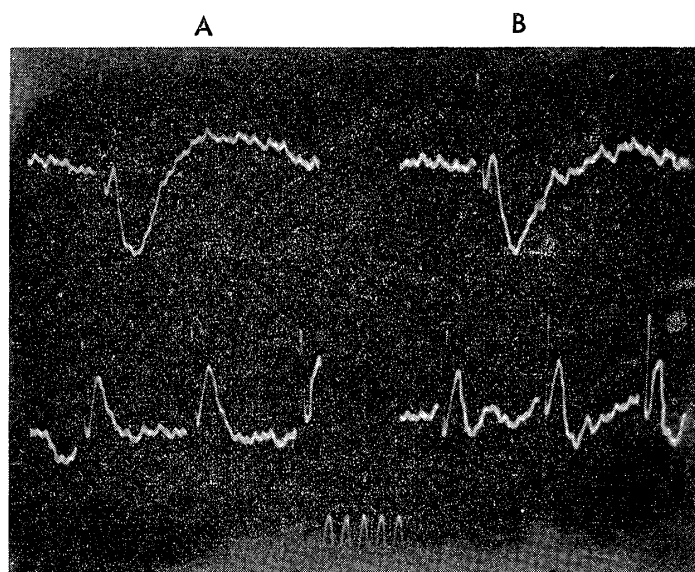


Fig. 2. Effect of chlorpromazine on single shock potential and post-tetanic potentiation recorded from hippocampus following single or repetitive stimuli of fornix.

Upper traces: potential evoked by single shock.

Lower traces: potentiation produced by repetitive stimuli.

A: control, B: 15 min. after 1 mg/kg chlorpromazine. Calibration: $100 \mu\text{V}$ and 50 c/sec.

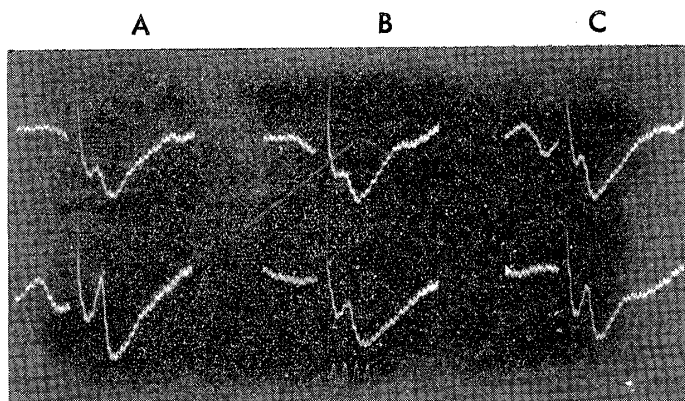


Fig. 3. Effect of chlorpromazine on single shock potential and post-tetanic potentiation recorded from hippocampus following single or repetitive stimuli of basolateral nuclei of amygdala.

Upper traces: potential evoked by single shock.

Lower traces: potentiation produced by repetitive stimuli.

A group: control, B group: 15 min. after 1 mg/kg chlorpromazine. C group: 60 min. after administration of drug.

Note a suppressive effect of chlorpromazine on potentiation following repetitive stimuli of amygdala.

Calibration: $100 \mu\text{V}$ and 50 c/sec.

frequently observed than recruitment during and after repetitive stimulation (10/sec).

One mg/kg of chlorpromazine depressed a development of potentiation without any effect on a single shock potential (Fig. 3). This effect continued about 60 to 90 minutes.

Hexobarbital sodium 10 mg/kg depressed PTP and administration of metrazol (20 mg/kg) antagonized to hexobarbital effect.

3. Effects on efferent pathways from hippocampus to hypothalamus: Green and Adey¹⁾ found that single stimulation to the hippocampus evoked a potential in the hypothalamus and when the frequency of stimulation was changed to 10/sec a slight potentiation of the potential was seen.

After 1 to 3 mg/kg of chlorpromazine no significant effects were observed in these potentials.

Hexobarbital sodium in dose of 10 mg/kg exerted blocking action on the development of potentiation without affecting on single evoked potential.

Discussion

In this investigation the observation of Takagi et al.³⁾ on the action of several psychotropic drugs on the central nervous system of the cat has been extended to the limbic system.

Effects on hippocampal seizure discharges: Chlorpromazine in 1 to 3 mg/kg doses suppressed hippocampal afterdischarges induced by stimulation of the fornix.

The results obtained here agree with those of Killam et al.⁴⁾ but do not support the view of Gangloff and Monnier⁵⁾ that chlorpromazine enhances the duration of hippocampal seizures. It has been reported by Preston⁶⁾ and Takagi et al.³⁾ higher doses of chlorpromazine (35-40 mg/kg) produced seizure discharges in amygdaloid nuclei of the cat. The action of chlorpromazine on the hippocampus seems to be different from the action on the amygdala, although the authors did not determine the effect of higher dose of chlorpromazine on the hippocampus.

Hexobarbital sodium was the most effective blocking agent for hippocampal seizures. Similar data with pentobarbital had been reported for cats (Killam and Killam⁷⁾ and rabbit (Green and Shimamoto⁷⁾, Gangloff and Monnier⁵⁾).

Effects on afferent from fornix to hippocampus: Chlorpromazine had no significant effects either on the single shock response or post-tetanic potentiation after repetitive stimulation. On the other hand, chlorpromazine suppressed the hippocampal seizure discharges induced by repetitive stimulation of the fornix. These facts suggest that suppressive effect of chlorpromazine on the hippocampal seizures are not due to their depressive action on afferent pathway from the fornix, but due to their direct suppressive action on the excitability of the hippocampus itself.

Hexobarbital sodium caused a suppression on PTP without notable effects on single shock response.

Effects on afferent from amygdala to hippocampus: Chlorpromazine depressed the post-tetanic potentiation without affecting the single shock potential. The facilitatory after-effects of repetitive stimulation characterizing potentiation are derived from the increased central excitation of certain synapses due to summation phenomena which are produced by repetitive firing. Thus, it would be considered that chlorpromazine depresses the summation of facilitatory states in this amygdaloid projection system.

Hexobarbital sodium showed more marked blocking action on post-tetanic potentiation than that of chlorpromazine.

Effects on efferent from hippocampus to hypothalamus: Many efferent pathways from the hippocampus to adjacent structures have been reported by Green and Adey¹⁾. The authors have taken efferent pathway from hippocampus to hypothalamus, as a measure in order to determine the effect of psychotropic drugs on hippocampal influence to hypothalamus. Chlorpromazine caused no notable effect on this pathway. Hexobarbital sodium showed blocking action on a development of potentiation without effect on single shock potential.

General consideration: Chlorpromazine exerts a selective effect upon the hippocampus or the facilitatory mechanism (PTP) in the amygdaloid-hippocampal pathway. This selective effect stands in contrast with the diffuse suppressive action of hexobarbital.

The role of the PTP in the physiology of the nervous system is unknown. There are, however, many suggestions that potentiation plays a major role, even possibly in the sphere of perception and learning. The changes in PTP studies are long lasting and in the direction of increased responsiveness. Also, there is psychophysical evidence in the visual and auditory systems for PTP (Hughes⁹⁾).

The findings obtained here may provide a neurophysiological basis for clinical effects of chlorpromazine.

Further studies on the effect of other psychotropic drugs on the limbic system are in progress.

Summary

1. The effects of chlorpromazine on the afferent and efferent pathways of the hippocampus were investigated and compared with that of hexobarbital sodium.
2. Chlorpromazine and hexobarbital sodium suppressed the hippocampal seizures induced by repetitive stimulation of the fornix.
3. Single shock response or post-tetanic potentiation recorded from the hippocampus following single or repetitive stimulation of the fornix were not depressed by chlorpromazine.

Hexobarbital sodium suppressed the development of potentiation without

any effect on single shock potential in this pathway.

4. Chlorpromazine and hexobarbital sodium selectively depressed post-tetanic potentiation following repetitive stimulation of amygdala without affecting single shock potential.

5. Effects of these drugs on the efferent pathway from the hippocampus to hypothalamus were investigated. Chlorpromazine had no significant effects on this pathway. Hexobarbital sodium suppressed the development of potentiation of the hypothalamic response following repetitive stimulation of the hippocampus without notable effect on single shock response.

References

- 1) Green, J. D. and Adey, W. R.: EEG Clin. Neurophysiol. 8, 245-262 (1956).
- 2) Gloor, P.: EEG Clin. Neurophysiol. 7, 243-246, (1955).
- 3) Takagi, H., Yamamoto, S., Takaori, S. and Ogiu, K.: Jap. J. Pharmacol. 7, 119-134 (1958).
- 4) Killam, B. K., Killam, K. F. and Shaw, T.: Ann. New York Acad. Sc. 66, 784-805 (1957).
- 5) Gangloff, H., and Monnier, M.: Helv. Physiol. Acta 15, 83-104 (1957).
- 6) Preston, J. B.: J. Pharmacol. & Exper. Therap. 118, 100-115 (1956).
- 7) Killam, E. K. and Killam, K. F.: Brain Mechanism and Drug Action (Editor Field, W. S.) P. 71-94 Charles C. Thomas, Springfield (1957).
- 8) Green, J. D. and Shimamoto, T.: A. M. A. Arch. Neurol. & Psychiat. 68, 609-619 (1953).
- 9) Hughes, J. R.: Physiol. Rev. 38, 91-113 (1958).