Pharmacology Biochemistry & Behavior, Vol 10, pp 851–853 Printed in the U.S A

Delta 9-Tetrahydrocannabinol:[1] Elevation of Absolute Visual Thresholds of Rabbits

SHEENA E. ROSE[2], WILLIAM O. DWYER, ARTHUR L. YEHLE

Department of Psychology, Memphis State University, Memphis TN 38152

(Received 13 March 1979)

ROSE, S. E., W. O. DWYER AND A. L. YEHLE. *Delta 9-tetrahydrocannabinol: Elevation of absolute visual thresholds of rabbits* PHARMAC. BIOCHEM. BEHAV. 10(6) 851–853, 1979.—The effect of Delta 9-tetrahydrocannabinol (THC) on the ability of rabbits to detect a minimal light stimulus (absolute visual threshold) was examined using the method of limits with an aversive classical conditioning paradigm. Both of two dosage levels of THC, similar to an amount ingested by a human from a single cigarette, significantly elevated the absolute visual threshold of all animals Normal baseline thresholds, however, returned with 24 hours.

Delta 9-tetrahydrocannabinol Absolute visual threshold Rabbits Aversive classical conditioning

DURING the past decade there has been considerable research interest in the effect of Delta 9-tetrahydrocannabinol (THC) on visual functioning. THC, the active constituent in marijuana, has been associated with distortions in subjective visual processes, although there is some contradictory evidence as to the nature and degree of its effects [1]. In addition to subjective perceptual phenomena, a few psychophysical studies have also assessed the effect of THC on some of the standard visual functions. Studies have shown that THC reduces visual acuity, has variable effects on critical flicker frequency, and does not affect the differential visual threshold, form discrimination or color vision [2, 12, 14, 18, 19].

With respect to absolute visual threshold, no human or animal data are available which demonstrate the influence of THC under conditions in which dosage levels were known and highly controlled. However, reports do exist on the influence of other similar drugs on visual threshold. LSD, for example, was found to elevate thresholds in both humans and pigeons [3,5], and amphetamine was found to significantly lower the absolute visual threshold in albino rabbits [17].

There is experimental evidence regarding the effect of THC on the neural system which could be interpreted as indicating its potential influence on the absolute visual threshold. It is known that, among other things, THC serves to lower the turnover rate of 5-hydroxytryptamine (5-HT), a transmitter substance in the central nervous system and the lateral geniculate nucleus of the thalamus is one of the areas in which 5-HT is concentrated [9, 11, 20]. Studies have shown that when this transmitter system is interfered with directly in the geniculate, evoked responses to a single light flash are inhibited [7,22]. It has been demonstrated that THC causes maximal alterations of 5-HT concentration in the rat midbrain, as opposed to the cortex and further, that THC concentrates heavily in the monkey visual system, especially in the lateral geniculate, as soon as 15 minutes after THC administration [11,13]. Other studies supporting the notion that THC can block sensory input in the geniculate have been reported in which single cells in the rat lateral geniculate, which normally respond to a single light flash, were inhibited by 200–300 micrograms of THC [2].

The purpose of the present study was to provide needed data on the effect of THC on the absolute visual threshold. Measurements were made on albino rabbits, by employing a classical conditioning technique previously shown to be suitable for use in studies investigating the effect of drugs on sensory behavior [6,15].

METHOD

The experiment called for a shock stimulus (US) to be delivered to the rabbits' eyelid, in combination with a white light stimulus flash (CS). Measurements of eyeblink activity were then obtained by recording changes in muscle potential. The light flash was delivered through an optical system containing an incandescent source, lenses, neutral density and polaroid filters, a shutter and fibre optic bundle, the end of which was held in a fixed position directly in front of the rabbits' right eye by means of a holder surgically mounted on the rabbits' skull. The duration of the CS was 0.7 seconds and it subtended a retinal angle of 17°.

Two dual purpose shock and recording electrodes were fashioned from small steel dress hooks and placed on the rabbits' upper and lower eye lids. These electrodes were used first to deliver a 3 mA shock which produced the blink response (UR), and then to record the marked change in potential caused by the muscular contraction of the lids. A

[1]Delta-9-tetrahydrocannabinol (THC) was obtained from the National Institute of Mental Health.
[2]The study was conducted by this author in partial fulfillment of the requirements for the Doctor of Philosophy degree

standard shock generator was used to produce the shock and a Model 7 Grass polygraph was used to record the eye blinks.

The rabbits were run in a Plexiglas rabbit restraining box which was housed in a dark, ventilated and sound attenuated chamber.

After a half hour of dark adaptation, each rabbit was initially classically conditioned to respond with an eye blink to a light flash, in the following manner. The light (CS) was presented for 0.7 sec and 0.4 sec after its onset, a 3 mA shock (US) was delivered to the rabbit's eye lid for 0.3 sec. Thus, the CS and US were terminated simultaneously. The training sessions were repeated on a daily schedule until each of the 8 rabbits reached a criterion of 100% conditioned responding to a CS of relatively low retinal illuminance (−1.00 log millilamberts).

Using the psychophysical method of limits (0.1 density steps), absolute thresholds were then determined for each of the rabbits. The threshold for a given rabbit was judged to be stable when the average thresholds obtained on three consecutive days were not significantly different from each other.

The 8 rabbits were then assigned to one of 2 groups: a low THC dosage group (0.025 mg/kg), and a high dosage group (0.50 mg/kg). The experimental sessions were conducted using the following format: On the first day all groups were run to determine a baseline for each rabbit. On Day 2 the rabbits were injected with the vehicle (propyleneglycol, Tween 80, and saline), dark adapted and one hour after injection absolute thresholds were obtained from them using the previously mentioned procedure. On Day 3 the two experimental groups were injected with the low THC and high THC dosages respectively and the thresholds were obtained. After a six day rest period, the same three day sequence was repeated a second time after another six days a third time and so on until a total of five replications were conducted.

RESULTS

The threshold values for the two groups were averaged across animals and replications and are presented in Fig. 1. They indicate a marked elevation in absolute threshold after injection of THC; the mean increase for the low dose group was 0.89 millilamberts and that for the high dose group was 1.50 millilamberts. *T*-tests used to compare thresholds under baseline, vehicle and THC conditions show that in both groups the vehicle injections did not significantly alter the threshold value, while the THC injections did ($p<0.01$). Futhermore, it is clear that the threshold is dose dependent because the mean threshold for the high dose group (−2.84 log millilamberts) is significantly higher than that for the low dose group (−3.57 log millilamberts), ($p<0.01$).

An analysis of variance performed on the threshold values showed no main effect due to experimental sessions, indicating there were no cumulative changes in thresholds measured under any of the experimental conditions (baseline, vehicle, THC). Thus, there was no apparent residual effect of the THC on the absolute thresholds. It also appears that the effects of the drug diminish fairly rapidly; threshold measurements were made on two animals (one high dose and one low dose) 24 hours after the fifth injection of THC, and *t*-tests indicated that both animals' thresholds had returned to baseline.

In spite of the marked changes in threshold produced by the THC, the drug had no effect on either the unconditioned eye blink response, or the topography and latency of the conditioned response. Nor were there any observable effects on the rabbits' pupil size.

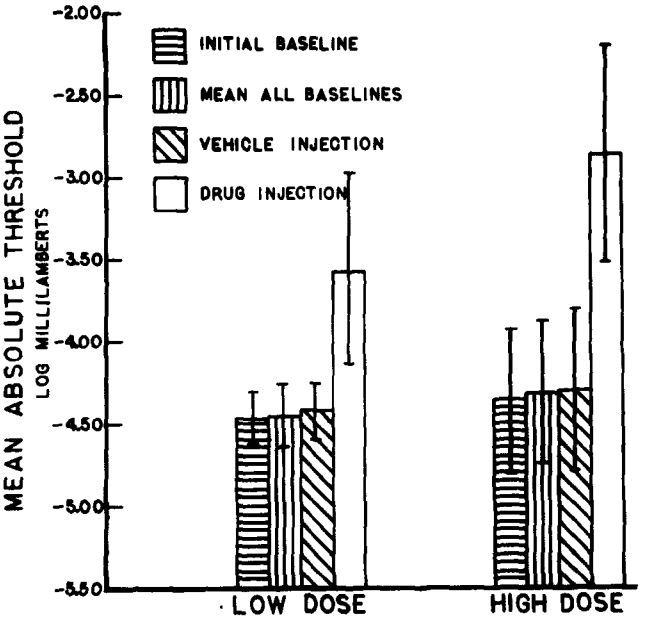

FIG. 1. Mean absolute visual thresholds of rabbits showing initial baselines, baseline days, vehicle injection days and drug injection days for the low dose (0.025 mg/kg) and the high dose (0.50 mg/kg) groups. Measurement variability indicated is ± 1.0 SD

DISCUSSION

The present finding that even low dosages of THC serve to elevate the absolute threshold in rabbits suggests at least one basis for the subjective, often vague, reports of visual alterations by human users. These findings are particularly meaningful in light of the fact that many previous animal studies have been criticized for employing dosages of THC which would be much higher than the average amount of the substance ingested by social users. Nahas [16] estimates the quantity of THC in a single cigarette to range from 1.87 to 66.0 mg and that approximately 50% of this amount is ingested by the smoker, an amount which is equivalent to a range of from 0.01 mg/kg to 0.47 mg/kg and is similar to the dosages used in the present study.

The findings that THC inhibits light sensitive neurons in the lateral geniculate nucleus of the thalamus [2], that LSD blocks geniculate responding to a light flash [10], and that both THC and LSD may act through decreasing turnover of 5-HT (heavily concentrated in the LGN) [11,23], provides evidence that the threshold shifts found in the present study may have been caused by altered LGN activity.

Another possible explanation for the present findings would be that THC acting through the reticular formation, affected the rabbits' attention mechanism thus causing an elevated threshold. However, Wallach and Gershon [24] observed no changes in the reticular multiple unit recordings obtained from cats which had been injected with THC (2.4 and 8.0 mg/kg). Domino [8] also ruled out THC effects on reticular activity; he found that dimethyl-heptyl-pyran, a THC analogue, depressed a conditioned photic driving re-

sponse in dogs in a study where a light flash was used as the CS and shock as the US. He interpreted his findings as indicating a change in the visual system itself, not an alteration of attention mechanisms. Thus, there is empirical justification for believing that the present findings are not a function of attention deficits produced by THC. Rather, the elevated thresholds are probably caused by the direct effect of THC on the visual system and, specifically on the activity in the lateral geniculate nucleus.

REFERENCES

1. Barber, T. *LSD, Marihuana, Yoga and Hypnosis*. Chicago: Aldine, 1970.
2. Bieger, D. and C. Hockman. Differential effects produced by D-9-tetrahydrocannabinol on lateral geniculate neurones. *Neuropharmac.* **12:** 269–273, 1973.
3. Blough, D. Some effects of drugs on visual discrimination in the pigeon. *Ann. N. Y. Acad. Sci.* **66:** 733–739, 1957.
4. Caldwell, D., S. Meyers, E. Domino and P. Merriam. Auditory and visual threshold effects of marihuana and man. *Percept. Mot. Skills* **29:** 755–759, 1969.
5. Carlson, V. The effect of lysergic acid diethylamide (LSD-25) on the absolute visual threshold. *J. comp. physiol. Psychol.* **51:** 528–531, 1958.
6. Cholewiak, R., R. Hammond, I. Seigler and F. Papsdorf. Effects of strychnine priphate on classically conditioned nictitating membrane responses of rabbits. *J comp. physiol Psychol.* **66:** 77–81, 1966.
7. Curtis, D. and R. Davis. Pharmacological studies upon neurones of the lateral geniculate nucleus of the cat. *Br. J. Pharmac* **18:** 217–246, 1962.
8. Domino, E., H. Hardman and M. Seevers. Central nervous system actions of some synthetic tetrahydrocannabinol derivatives. *Pharmac. Rev* **23:** 317–335, 1971.
9. Evarts, E. Experimental analysis of the inhibitory action of lysergic acid diethylamide. *Am. J. Physiol* **182:** 594, 1955.
10. Evarts, E , W. Landau, E. Freygang and W. Marshall. Some effects of lysergic acid diethylamide and burotenine on electrical activity in the cat's visual system. *Archs Neurol Psychiat* **74:** 49, 1956.
11. Johnson, K. and W. Dewey. The effect of delta 9-tetrahydrocannabinol on the conversion of 3-H-tryptohan to 5-H-hydroxytryptamine in the mouse brain. *J. Pharmac. exp. Ther.* **207:** 140–150, 1978.
12. Keeler, M., J. Ewing and B. Rouse. Hallucinogenic effects of marijuana as currently used. *Am. J. Psychiat* **128:** 213–216, 1971
13. McIsaac, J., R. Fritchie, A. Idanpaan, H. Ho, A. Heikkita and E. Englert. Distribution of marihuana in monkey brain and concommitant behavioral effects. *Nature* **230:** 593–594, 1971.
14. Moskowitz, H., S. Sharma and W. McGlothin. The effect of marihuana upon peripheral vision as a function of the information processing demands on central vision. *Percept. Mot. Skills* **35:** 875–882, 1972.
15. Peel, W. and A. Yehle. Differential effects of d-amphetamine in classical discrimination conditioning of rabbits. *Psychon. Sci* **14:** 210–211, 1969.
16. Nahas, G. *Marihuana—Deceptive Weed*. New York: Raven Press, 1973.
17. Rose, S. The effects of amphetamine on the absolute visual threshold of classically conditioned albino rabbits. Unpublished Master's Thesis, Memphis State University, Memphis TN 1971.
18. Schwin, R., S. Hill, D. Goodwin and B. Powell. Marihuana and critical flicker fusion. *J. nerv. ment Dis* **158:** 142–144, 1974.
19. Shapiro, D. The occular manifestations of the cannabinols. *Ophthalmology* **168:** 366–369, 1974.
20. Sofia, R., B. Dixit and H. Barry. Effect of delta-9-tetrahydrocannabinol on serotonin metabolism in the rat brain. *Life Sci.* **10:** 425, 1971.
21. Tart, C. Marihuana intoxication: common experiences *Nature* **226:** 21–29, 1970.
22. Tebecis, A. and A. DiMaria. A re-evaluation of the mode of action of 5-HTP on lateral geniculate neurons: comparison with catecholamines and LSD. *Expl Brain Res.* **14:** 480, 1971.
23. Tonge, S. and B. Leonard. The effects of some hallucinogenic drugs on the metabolism of 5-hydroxytryptamine in the brain. *Life Sci.* **8:** 805–814, 1969.
24. Wallach, M. B. and S. Gershon The effects of D-9-THC on the EEG reticular multiple unit activity and sleep of cats. *Eur J Pharmac.* **24:** 172–178, 1973.