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STEREOTYPED BEHAVIOR AND CYCLIC CHANGES IN RESPONSE PRODUCED BY LSD IN GOATS

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Summary—The ambulation of adult female goats was studied in a modified open field test before and after injections of lysergic acid diethylamide (LSD) in doses of 7·5 or 15 μg/kg body weight. Under the influence of LSD, the animals increased their ambulatory activity and developed stereotyped walking patterns, e.g. squares, circles, figure 8's, or ovals. Each pattern was found to be specific for each animal and did not change with subsequent injections. The stereotyped walking patterns further support the view of a stabilizing and, indeed, a rigidifying action of LSD on behavior. With successive injections of LSD at intervals of 24, 48, 72 or 96 hours, the reaction to the drug fluctuated rhythmically. The cyclical pattern consisted of periods during which the drug sensitivity gradually declined and then abruptly rose to the original level. The pattern of tolerance and loss of tolerance which accompanies repeated doses of LSD suggests mobilization and periodic breakdown of an endogenous anti-LSD mechanism.

INTRODUCTION

THE goat's ambulatory pattern in its quantitative and qualitative aspects has been shown to be a sensitive indicator of anxiety, of the residual effects of early stress (LIDDELL, 1961) as well as of psychotropic drugs (A. U. MOORE, personal communication). The present study was undertaken to investigate the influence of LSD in single and repeated doses on the walking pattern of goats.

METHODS

Adult goats, ranging in body weight from 27 to 59 kg, were studied in a modified open field test adapted from a method previously described by LIDDELL and his associates (1961, 1962). A lightweight harness was strapped around the chest and connected via a nine-foot aluminum rod (total weight 200 gms) to a universal joint mounted in the center of the ceiling of the $10' \times 10'$ uniformly-walled experimental room. The universal joint was provided with rollers which allowed the connecting rod to move up and down freely. The animal's movements along two orthogonal coordinates in the horizontal plane were transduced to rotating movements of the corresponding horizontal orthogonal axes of the joint and transmitted by lightweight rods and small universal joints to the rotors of a pair of transmitter selsyn motors. A pair of receiver selsyns mounted on a $4' \times 4'$ horizontal drawing table transmitted the angular displacements of the selsyn rotors by means of rods linked to a ball-point pen which recorded the walking pattern of the goat in the experimental room by a reduction factor of about 40 to 1. Pre-experimental tests showed that the system contained negligible distortion and little inertial lag.

Prior to the experiment, a polyethylene catheter was inserted in a large vein of one of the forelegs. At the beginning of each experiment, an animal was harnessed and allowed

to walk around the experimental room at will. The pattern, as well as distance of ambulation (i.e., length of the tracing measured in inches), was determined for six consecutive five-minute periods. After the control period, the drug was injected (i.v.) and observation and recording were continued for twelve five-minute periods. The tracing paper was changed at the end of each time interval. Total ambulation after drug administration was calculated by summing the distances determined in the twelve post-injection periods. During the experiment, the animals were observed either through a one-way window or through a small hole in the ceiling of the experimental room. The experiments usually were performed at night or early in the morning to avoid distractions.

RESULTS

During the control period, little or no locomotion was recorded, but after lysergic acid diethylamide (LSD) injection (15 μg/kg body weight), activity increased considerably. The effect became maximal 5 to 15 minutes after drug administration and then decreased during the next 60 to 90 minutes, often to a level less than that recorded for the control period (Fig. 1). Saline solution injections did not produce significant effects (Fig. 1).

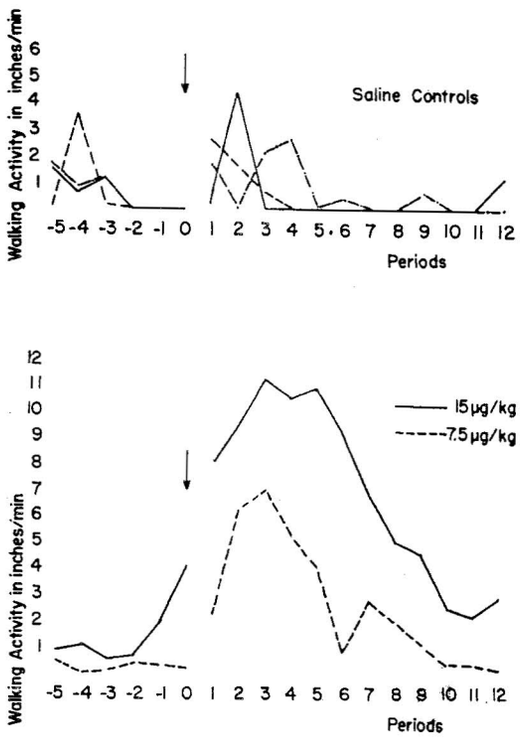

FIG. 1. Walking activity measured in inches per minute of tracing in response to saline solution and LSD in doses indicated. Top: walking activity in six 5-minute periods before, and twelve 5-minute periods after administration of saline solution (arrow); 3 different animals. Bottom: walking activity before and after i.v. injection of 7·5 and 15 μgm LSD per kg, respectively. Means of 3 animals in each dose group.

For identical doses of LSD, female goats produced greater reactions, lasting for longer periods than did male animals. For this reason we have used only females in these studies.

When LSD was administered daily, systematic changes in the effectiveness of the drug as evidenced by cyclical changes in walking activity were noted. Each cycle was characterized by progressive loss of LSD-induced hyperactivity followed by an abrupt rise to the original level (Fig. 2). To evaluate the conditioning effect of injection alone, an addi-

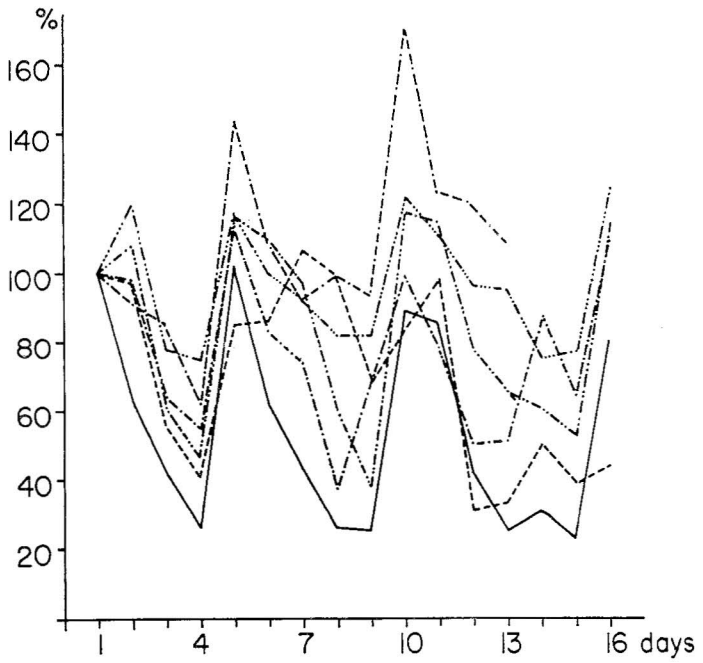

FIG. 2. Total walking activity of 5 animals in response to daily administrations of LSD (15 μg/kg) for 16 days, and of one animal treated for 13 days. These six experiments were conducted over a period of nine months. Note cyclic changes in drug response with peaks at days 1, 5, 10 and 16. Walking activity is expressed in per cent of first day values.

tional group of goats received four consecutive daily LSD injections followed by four consecutive injections of saline solution. No cyclical fluctuations of activity attended the injections of saline solutions (Fig. 3).

With longer intervals between injections (48, 72 and 96 hours, four injections in three animals for each interval group), a cyclical pattern was, *prima facie*, less apparent. Yet, if plotted on the same graph as the 24-hour series, the values of these longer interval series were not randomly scattered but rather followed the cyclical pattern of the 24-hour series (Fig. 3). An additional group, injected and tested at five-day intervals, showed a trend towards increased drug sensitivity, whereas a group of three animals injected at eight-day intervals showed negligible change in drug effect.

Five to ten minutes after the administration of LSD the majority of the animals produced tracings of rectangular shape, indicating clockwise or counterclockwise walking adjacent to the walls (Fig. 4). Some animals exhibited other types of stereotyped walking

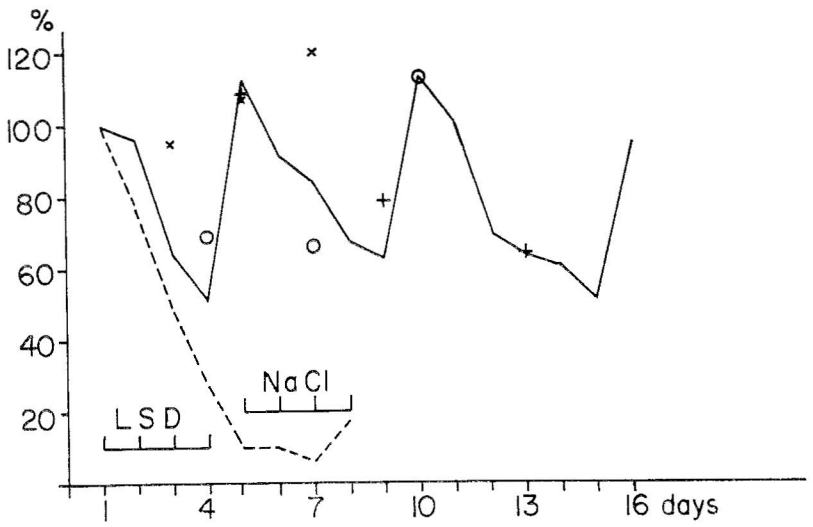

FIG. 3. Full line: mean values derived from experiments shown in Fig. 2. 0, + and X indicate values obtained in goats injected with 15 μg/kg at 48, 72 and 96 hour intervals respectively; 3 animals in each interval group. Dotted line: responses to 4 daily injections of LSD (15 μg/kg) followed by 4 daily injections of saline. Mean of 3 animals.

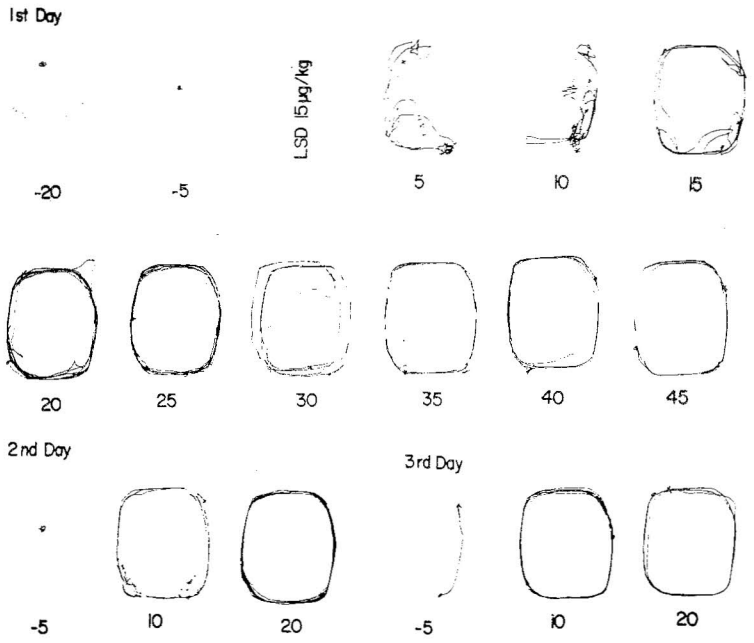

FIG. 4. Tracings of walking pattern of the goat. Top and middle rows: continuous record of nine 5-minute periods after injection of LSD. Two 5-minute control runs at 20 and 5 minutes prior to injection are also shown (–20 and –5). Note development of "squaring" 15 minutes after injection. Bottom row: one pre-injection and two post-injection records one and two days respectively after top row experiment in same animal, taken at 10 and 20 minutes after administration of LSD. Note similarity of pattern.

patterns, e.g., shapes such as squaring off of parts of the room, small ovals, figure 8's, L's or small circles (Fig. 5). The form of the stereotyped pattern appeared to be specific for each animal; repeated administration of the drug to the same goat always produced the same basic pattern (Figs. 4 and 6).

FIG. 5. Various shapes of stereotyped walking patterns in response to LSD.

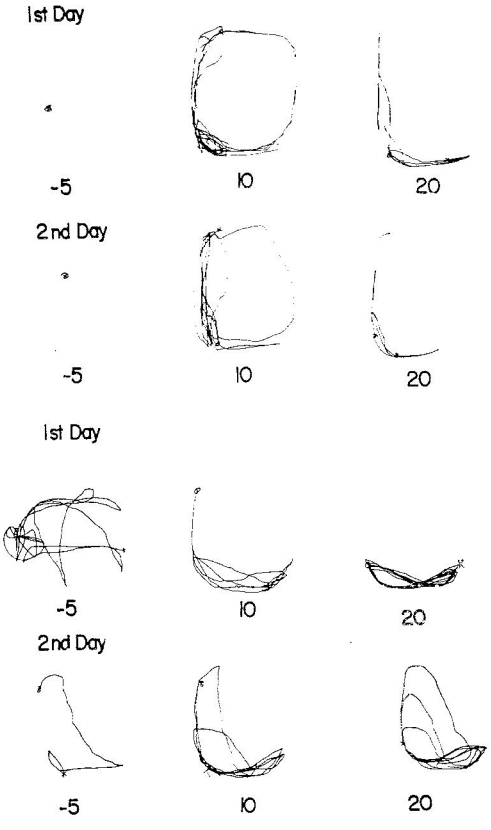

FIG. 6. Walking patterns in individual animals receiving repeated injections. "–5" refers to control run 5 minutes before injection. "10" and "20" refer to two runs 10 and 20 minutes respectively after administration of 15 μgm/kg LSD. "1st day" and "2nd day" refer to the two injections on two consecutive days. Top section: typical figure "L" animal. Bottom section: typical figure "8" animal.

DISCUSSION

The "stereotyped" walking pattern suggests increased stabilization, i.e., hyperhomeostasis, in systems that control ambulatory activity in the absence of directing stimuli. There is additional evidence that points to a hyperhomeostatic action of LSD: KOELLA and WELLS (1959) have reported that intravenous LSD reduces the variability of optically-evoked responses in the unanesthetized rabbit; EVARTS *et al.* (1955) has remarked on the greater stability of evoked responses after intracarotid administration of LSD in cats; GOLDSTEIN and his co-workers (1963) reported that in human subjects LSD–25 decreased the variability of alpha-waves without changing the mean alpha output significantly. The hyperhomeo-static effect of LSD in these systems has not been explained.

The oscillatory changes in walking activity after repeated injections of LSD are the manifestation of a cyclical alteration in reactivity of the organism to the drug. From our results, we conclude (1) that the oscillation is time-locked to the first injection, (2) that within limits the frequency is independent of the interinjection intervals, and (3) that the frequency of this oscillation is remarkably similar in all animals tested. The results from experiments in which saline followed LSD injections support the interpretation that the sudden increase in walking activity on the fifth day observed in the series with prolonged LSD administration is a true drug effect and cannot be related to the act of injection or to conditioning.

Using the WINTER–FLATAKER rat rope climb test (1951), PAWLOWSKI in our laboratory, found a similar pattern of oscillating sensitivity to LSD. In the rat, however, the periods were longer (7–8 days) and there was a marked tendency toward decay and damping of successive cycles (manuscript in preparation). Thus the oscillatory pattern can be demonstrated not only in two different species but in two dissimilar test situations. In ABRAMSON'S (1955) experiments involving the daily administration of LSD to humans, the drug effects decreased over a four-day period, but rose on the fifth day. His data are suggestive of cyclical changes in drug response but longer series are needed to establish the exact pattern.

The single periods of the cyclical pattern are asymmetrical, exhibiting gradual, quasi-exponential, falling phases and steep rising phases. An interpretation consistent with the data is that the oscillatory pattern is the manifestation of a gradual build-up of an anti-LSD factor, its sudden breakdown after four to five days, and thereafter, a rhythmical reoccurence of the two phases. Work is in progress to determine whether other bodily functions reveal such rhythmical changes in LSD sensitivity and whether such changes correlate with LSD concentrations in the brain and/or LSD metabolizing activity in the liver. Also, the effects of other compounds such as mescaline and amphetamine are now under investigation. The observation of cyclical response to the continued administration of a drug may have an important bearing on unexplained drug refractoriness and hypersensitivity in humans.

Résumé—Le présent travail porte sur l'activité ambulatoire de chèvres adultes étudiée grace à un test modifié d'activité en terrain ouvert, avant et après injections de diethylamide de l'acide lysergique (LSD), à des doses de 7, 5 ou 15 ug/kg de poids corporel. Sous l'influence du LSD les animaux augmentent leur activité ambulatoire et développent des figures de marche stéréotypée sous forme de carrés, de cercles, de huits ou d'ovales. On constate que chaque figure est spécifique d'un certain animal et qu'elle ne change pas au cours des injections suivantes. Ces figures de marche stéréotypée suggèrent le concept d'une action stabilisante, voire rigidifiante du LSD sur le comportement. Au cours d'injections successives de LSD à intervalles de 24, 48, 72 ou 95 heures, les réactions à la drogue présentent des fluctuations rythmiques. L'évolution

cyclique consiste en périodes durant lesquelles la sensibilité à la drogue décline graduellement et ensuite remonte brusquement au niveau original. Cette forme de tolérance et de perte de tolérance qui accompagne l'administration de doses répétées de LSD suggère une mobilisation et une dégradation périodique d'un mécanime endogène anti-LSD.

Zusammenfassung—Der Einfluss von LSD–25 auf die lokomotorische Aktivität von ausgewachsenen weiblichen Ziegen wurde in einem modifizierten Offen-Feld-Test untersucht. LSD–25 (7·5 and 15 μg/kg iv.) verstärkte die motorische Gehaktivität erheblich und die Tiere produzierten ein stereotypes, d.h. quadratisches, ovales, kreisförmiges, 8-förmiges oder L–förmiges Gehmuster, das sich auch bei wiederholter Applikation nicht änderte. Diese Stereotypie unterstützt die Auffassung, dass LSD–25 einen stabilisierenden Einfluss auf das Zentralnervensystem ausübt. Mit wiederholter Verabreichung entwickelte sich eine rhythmisch fluktuierende Aenderung der LSD-Wirkung. Jede einzelne Periode dieses Rhythmus bestand aus einer 4–6 Tage andauernden Phase während welcher die LSD-Sensitivität allmählich absank und einer kurzen Phase während welcher die Reaktivität sprungweise auf die Ausgangslage anstieg. Dieser Wechsel von zunehmender Toleranz und Resensibilisierung lässt vermuten, dass periodisch ein Anti -LSD-Faktor auf- und abgebaut wird.

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