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The Effect of LSD-25 on the Interaction between Conditioned and Non-conditioned Stimuli in a Simple Avoidance Situation

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With 2 Figures in the Text

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Introduction

Many studies have indicated that the alerting effect of small doses of d-lysergic acid diethylamide (LSD-25) is related to changes in the responsiveness of the animal to sensory stimuli. Bradley and Elkes (1956) observed that the degree of alertness following a dose of 15 μg/kg i.p. 'was dependent upon slight variations in the environment,' while Ursin (1962) noted that cats reacted 'very strongly to slight noises or movement in the environment' with doses as low as 5 μg/kg i.v. Decreased thresholds for auditory induced arousal responses after 1 to 8 μg/kg i.v. (Bradley and Key 1958) and marked increases in the generalisation of auditory stimuli after 15 μg/kg i.p. (Key 1961a) are also indicative of a change in responsiveness to sensory stimulation. In rabbits doses of 1 to 5 μg/kg i.v. 'facilitate the alerting response to even minimal stimuli' (Himwich 1957), while higher doses of 50 μg, administered by the subcutaneous route to rats, is said to sensitise the central nervous structures to afferent impulses (Taeschler et al. 1960).

Probably more significant is the fact that 5 to 15 μg/kg i.p. of LSD-25 may overcome the effect of habituation (Key and Bradley 1960), or produce a marked decrease in the rate of habituation to auditory stimuli (Key 1961b). Increased responsiveness to previously insignificant stimuli would imply heighthened distractability, especially in environments providing a moderate level of ambient sensory stimulation. Thus the confusional aspect of environmental changes occurring simultaneously with test stimuli could well induce alterations in response accuracy in discrimination prodecures, in timing behaviour, or in tests involving some measure of delay.

It was the purpose of this study to determine the effect of LSD-25 on the distractability of cats carrying out a simple conditioned avoidance response using the response time as a measure of the interaction of conditioned and non-conditioned stimuli.

Methods

Twenty adult cats, weighing between 2.5 and 4.0 kg were trained to cross a 23 cm (nine inch) high barrier on the presentation of a visual stimulus. Failure to accomplish the task within three seconds was punished by an electric shock of 0.5 mA delivered to the feet of the animal from a metal grid floor. The visual conditioning stimulus consisted of a series of five half second flashes of light at an intensity of 40 lumens per square metre delivered over a period of 4.5 seconds from eight lights situated in the roof of the cubicle in which the cats were trained and tested. The cubicle had a background illumination of 10 lumens per square metre and was sound-proofed to provide a minimum attenuation of 80 db for frequencies within the range 100—20,000 c/sec. Low frequency vibration conducted via the floor of the room housing the cubicle was minimised by the use of rubber blocks and a false floor suspended within the cubicle. The temperature was controlled by a noiseless ventilation system and the cat observed by means of a closed-circuit television system with the camera in the roof of the cubicle. Tones or noise could be presented to the animal from a loudspeaker, also situated near the roof of the cubicle.

Each animal was trained for 40 trials each day on consecutive days until acquisition of the response was attained. Twenty minutes after the intraperitoneal injection of 0.5 ml of normal saline, the response time taken to cross the hurdle from the initiation of the conditioning stimulus was measured. Trials were conducted at the rate of one every one to two minutes and the visual conditioning stimulus presented either alone or simultaneously with a series of tonal pips at different intensities. The frequency of the tonal pips was 3,000 c/sec, the duration 25 msec and the rate five per second. Three intensities, differing in increments of 18 db were employed, the loudest tone being approximately 72 db above the human threshold of hearing. For this reason the intensities are marked in the text as 36, 54 and 72 db. No punishment was given for incorrect responses and the trials in which the visual stimulus, or the visual stimulus plus tonal pips were given, were presented in random order. Ten trials were conducted at each level of auditory stimulation, with appropriate control runs. Trials in which the animal failed to cross the hurdle or crossed some fifteen seconds following the end of the conditioning stimulus were discounted and only correct responses used to measure the response time. Two weeks after the control test the animals were retrained to the 100% correct response level. They were then divided randomly into two groups of ten, one group receiving 10 μg/kg and the other 20 μg/kg of LSD-25 by the intraperitoneal route. Twenty minutes after the injection the response time for the avoidance response, with and without the distractive influence of the tonal pips, was again measured using the same procedure as in the control. For statistical purposes each animal was used as its own control and the significance of the difference between the response times before and after the drug administration was determined for each intensity of the tone by using the Student 't' test for correlated data.

Results

Effects of LSD-25 on response time

Once the 100% correct response level had been attained the time taken to cross the hurdle from the initiation of the visual stimulus was quite constant, even taking into consideration that the trials were conducted without reinforcement. The distractive influence of the tonal pips presented simultaneously with the conditioning stimulus produced a significant ($P = .01-.001$) lengthening of the response time (Fig. 1 A and B). In both groups of animals a similar pattern emerged. At the lower intensity of auditory stimulation (36 db) the response time fluctuated, since the addition of the tonal pips produced either no effect or markedly prolonged the time taken to cross the hurdle. On the other hand, at the two higher intensities (54 and 72 db) the response time was relatively stable. The presentation of the tonal pips with the visual conditioning stimulus appeared to arrest the movement of the animal until just before or at the end of the stimulus, when it crossed very quickly. The resultant response times for both groups therefore, approximated very closely to the duration of the conditioning stimulus, that is 4.5 seconds (Fig. 1 A and B).

The effect of a single dose of 10 μg/kg of LSD-25, administered by the intraperitoneal route was twofold. Firstly, it produced a significant decrease ($P = .01-.001$) in the time taken to cross the hurdle on the presentation of the visual conditioning stimulus alone (Fig. 1 A). Secondly, it potentiated the distractive influence of the tonal pips. At all three levels of auditory stimulation significant increases in the response times occurred (Fig. 1). Moreover, the response times were related to the intensity of the tonal pips, a small increase at the 36 db level ($P = .05$) increasing to a maximum at the 72 db level ($P = .01-.001$).

A twofold change also occurred after a single dose of 20 μg/kg i.p. but in this case the effect produced was not so marked. Response times for the avoidance behaviour initiated by the visual stimulus alone decreased by a mean of only 18% as opposed to the 29% observed after the smaller dose of 10 μg/kg i.p. of LSD-25. The distractive influence of the tonal pips was again potentiated by 20 μg/kg, but the relationship between response time and the intensity of the tone was abolished. The times fluctuated considerably, being either relatively short and approximating to control values, or 5 to 8 seconds in excess of the duration of

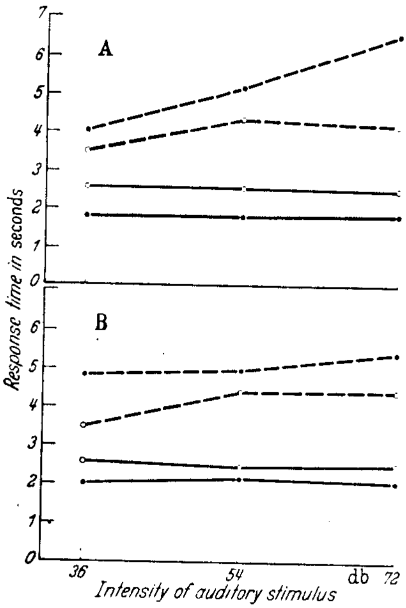

Fig. 1

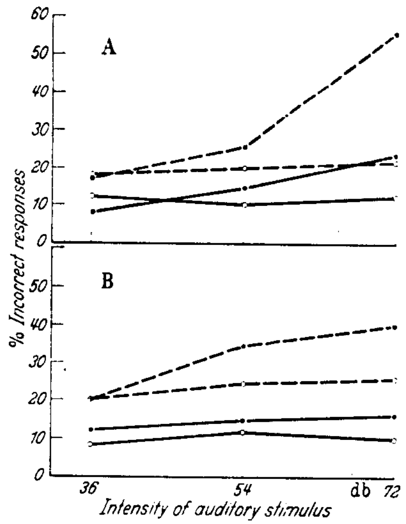

Fig. 2

Fig. 1 A and B. The effect of LSD-25 on the response time of a simple visually conditioned avoidance response initiated with and without the distractive influence of an auditory stimulus. Time taken to cross the hurdle on the presentation of the visual conditioning stimulus before o——o, and after •——• the administration of 10 μg/kg i.p. (A) and 20 μg/kg i.p. (B). Time taken to cross the barrier on the presentation of the visual conditioning stimulus and the series of tonal pips at three different intensities before o - - - o and after • - - - • 10 μg/kg i.p. (A) and 20 μg/kg i.p. (B)

Fig. 2 A and B. The effect of distraction and LSD-25 on the accuracy of response of a simple visually conditioned avoidance response. Number of incorrect responses before o——o and after •——• the administration of 10 μg/kg i.p. (A) and 20 μg/kg i.p. (B) LSD-25. Number of incorrect responses resulting from the simultaneous presentation of a series of tonal pips at three different intensities with the visual conditioning stimulus before o - - - o and after • - - - • the administration of 10 μg/kg i.p. (A) and 20 μg/kg i.p. (B) LSD-25

the conditioning stimulus. However, the overall effect was an increase in response times, being more marked at the lowest intensity of auditory stimulation ($P = .001$) than at the 72 db level ($P = .05$).

Effect of LSD-25 on the accuracy of response

It is to be expected that incorrect responses will occur in tests repeatedly carried out without reinforcement. In the present study the mean number of failures in the control series for each group of animals was approximately 10% (Fig. 2), whereas the distractive influence of the tonal pips yielded a higher number. The largest rise of 20 to 25% occurred with the highest intensity of auditory stimulation (Fig. 2). It would also be expected that the inhibitory effect of the tonal pips, giving rise to a higher percentage of failures would facilitate extinction of the response, or at least adversely influence the response times in the trials where only the visual stimulus was presented. The control trials, however, both in response times and the incidence of incorrect responses, were surprisingly stable with little interaction between tests (Fig. 2).

After 10 μg/kg i.p. of LSD-25 a rather different picture emerged (Fig. 2A). A potentiation of the distractive influence of the tonal pips was indicated by an increase in the number in incorrect responses at the highest intensity of auditory stimulation. Moreover, the increased confusion of the animal, although not being indicated in the response times, was also shown by the increase in the number of failures in the control trails for this level of tonal pips. (Fig. 2A). The change occurred irrespective of the order in which the different intensities of auditory stimulation were presented.

After 20 μg/kg i.p. of LSD-25 there was again in increase in the number of incorrect barrier crossing responses. There was also a tendency in the control trials for the number of failures to increase when compared with pre-drug control levels. These changes, although small and not significant, demonstrated the possibility of interaction between the conditioned responses initiated with and without the auditory stimulation. The fact that these alterations, as in the group of animals receiving 10 μg/kg i.p., occurred irrespective of the experimental procedure and were not accompanied by any significant changes in the response times of correct responses illustrated that extinction of the avoidance response due to repeated presentation of the un-reinforced conditioning stimulus was not the causative factor.

Discussion

The simultaneous presentation of a series of tonal pips with the visual conditioning stimulus prolonged the time taken to carry out a previously learned simple conditioned avoidance response. The delay incurred in crossing the hurdle from one of side of a sound-proofed cubicle to the other was related to the intensity of the auditory stimulus. Doses of 10 and 20 μg/kg i.p. of LSD-25 potentiated the distractive influence of the tonal pips, as indicated by a further increase in both response times and the number of incorrect responses. This change was in contrast to the effect produced when the visual conditioning stimulus was presented alone, for in this case there was a decrease in the time taken to cross the hurdle. It would appear therefore, that the alterations induced by LSD-25 in the response time of a simple conditioned avoidance response are twofold, depending upon the presence or absence of sensory information other than that of the conditioning stimulus. Similar conclusions may be drawn indirectly from the experiments of FUSTER (1956). Monkeys trained to recognise stereometric objects showed impaired recognition and a lengthening of response time when a tone was presented simultaneously with a short flash exposure of the stimulus object. LSD-25 in low doses (5 to 10 μg/kg), produced similar impairment in both accuracy of performance and response time without effecting response rate. In a series of psychological tests using human subjects ABRAMSON (1955) was able to show that 100 μg of LSD-25 adversely affected reaction time to visual and auditory stimuli, while other experiments (JARVIK et al. 1955) demonstrated that a similar dose of LSD-25 produced changes in abstract thinking and the ability to concentrate. Increased responsiveness to previously insignificant stimuli (KEY and and BRADLEY 1960; KEY 1961a) would imply heightened distractability and thereby impairment in concentration or prolonged attention. Indeed, the results of the present study show that in cats LSD-25 increases the distractive influence of stimuli presented simultaneously with the conditioning stimulus. Such changes may have important repercussions in a variety of specific test procedures, especially those carried out in environments providing a moderate level of ambient sensory stimulation. For example, JARVIK and CHOROVER (1960) were unable to explain an impairment in the accuracy of performance of monkeys carrying out a delayed alternation task after only .005 mg/kg i.m. of LSD-25, but suggested that an increased susceptibility to the distractive influence of ambient sensory stimuli may make a subject less capable of handling a delay type of situation.

One other point to consider in the effect produced by LSD-25 is the dose level employed. In the present study 20 μg/kg i.p. caused a decrease in the response time of the avoidance behaviour initiated by the conditioning stimulus alone, which although significant, was less marked than that produced by a smaller dose of 10 μg/kg i.p. The number of incorrect responses in these control trials was also slightly increased. Extinction of the conditioned response could account for such changes, but it would be expected that the greater number of failures and any increases in the response time would occur towards the end of the experiment. This was not the case. The dose/effect characteristics of LSD-25, with regard to the reaction time of simple conditioned avoidance behaviour has been studied by TAESCHLER et al. (1960). In rats the reaction time was significantly decreased by doses of 50 to 200 μg/kg administered by the subcutaneous route, while higher doses restored the times to control or above controls levels. The rather high doses necessary to produce the initial change is probably due to the route of the injection, but nevertheless they demonstrate that the effect produced by LSD-25 is related to the dose. In the present study the decreased effectiveness of 20 μg/kg i.p. of LSD-25 and the fluctuations in response level may indicate the beginning of a transitional phase between the alerting and facilitatory effect induced by small doses and the sedation (HIMWICH 1957) and blocking of conditioned behaviour (COOK and WEIDLEY 1957) known to occur with the higher doses.

In conclusion it would appear that LSD-25, in small doses (10 to 20 μg/kg i.p.), decreases the response time for a simple conditioned avoidance response if the distractive influences of other sensory information is relatively low. In environments providing a moderate level of ambient stimulation, increases in response time can be expected due to the increased distractability of the animals.

Summary

The distractive influence of a series of tonal pips presented simultaneously with a visual conditioning stimulus was assessed using the time taken to carry out the simple conditioned avoidance response as a measure of the interaction between the conditioned and non-conditioned stimuli. Presentation of the tonal pips at three different levels of intensity induced a lengthening of response time, which was potentiated by 10 and 20 μg/kg i.p. of LSD-25. When the conditioning stimulus was presented alone, however, a decrease in response time occurred after the drug had been given. The introduction of the auditory stimulus also produced a slight increase in the number of incorrect responses. Again LSD-25, at both dose levels, potentiated the change and induced an increase in the number of failures. The effect produced by LSD-25 on the response time for a simple conditioned avoidance response, therefore, appears to depend upon the presence or absence of stimuli other than used in the conditioning procedure.

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