Pharmacology Biochemistry & Behavior, Vol. 3, pp. 861–868.

Effects of Lysergic Acid Diethylamide (LSD) on Temporal Recovery (Pre-Pulse Inhibition) of the Acoustic Startle Response in the Rat[1]

MICHAEL DAVIS[2] AND MICHAEL H. SHEARD

Yale University School of Medicine and Connecticut Mental Health Center
New Haven CT 06508

(Received 12 November 1974)

DAVIS, M. AND M. H. SHEARD. *Effects of lysergic acid diethylamide (LSD) on temporal recovery (pre-pulse inhibition) of the acoustic startle response in the rat.* PHARMAC. BIOCHEM. BEHAV. 3(5) 861–868, 1975. – In a series of 6 experiments 40 μg/kg d-lysergic acid diethylamide (LSD) augmented acoustic startle amplitude in rats when long intertone intervals (4, 8, 16, or 32 sec) were used but not when short interstimulus intervals were used (0.02, 0.1, 0.5, 1, or 2 sec). In contrast, 8 mg/kg d-amphetamine augmented startle when either long or short interstimulus intervals were used. The results suggest that LSD augments startle by accelerating the decay of pre-pulse inhibition (temporal recovery process) which may be one mechanism by which LSD can alter sensory processing.

Startle D-Lysergic acid diethylamide LSD Pre-pulse inhibition Temporal recovery process Recovery cycles Habituation Amphetamine

AMONG the most dramatic effects of d-lysergic acid diethylamide (LSD) are the changes it produces in sensory perception. Words such as vivid, intense, or fluid are frequently used to describe the world, particularly the visual world, as it appears after LSD [13]. One possible explanation for these perceptual changes is that LSD may allow the reception of a greater number of sensory stimuli per unit time and/or increase the subjective intensity of incoming sensory information.

To account for the changes in sensory perception that occur after LSD it has been proposed that LSD interferes with habituation [20]. For example, Key and Bradley [20] showed that a stimulus which initially provoked EEG arousal in sleeping cats failed to do so after several repetitions. As soon as a minute dose of LSD (5 μg/kg) was injected, however, that same stimulus or even much less intense stimuli now provoked EEG arousal. The conclusion was that LSD interfered with the normal process of habituation. It was also shown, however, that in animals which were not habituated to the arousing stimulus, the same dose of LSD also decreased the threshold for EEG arousal. Since in this case, no habituation had yet occurred, it would be difficult to conclude that LSD affected sensory perception by interfering with habituation.

Using the acoustic startle response in the rat as an index of excitability to sensory stimulation, Miliaressis and St-Laurent [23] found that doses of 60, 120 or 240 μg/kg LSD vs saline resulted in augmented startle amplitude when loud tones were repetitively presented 30–40 min after injection. When the initial startle levels of the various groups were set to a common value of 100 percent, subsequent rates of percentage decrement were slower in the LSD groups than in the saline group. Based on this observation it was concluded that LSD interfered with habituation. It was also the case, however, that startle levels to the first several tones (that is before any habituation had occurred) were higher in the LSD groups as well and the absolute decrease in startle amplitude was the same or even greater in the LSD groups compared to the saline group. Again, the increase in startle amplitude to the initial tones would be difficult to attribute to impaired habituation, since habituation had not yet occurred.

At about the same time it was found that doses of 20, 40 or 160 μg/kg LSD also augmented the amplitude of the acoustic startle response [9]. More important, it was shown that the increase in startle amplitude to the very first tones the animal had ever heard resulted from increased sensitization to background noise, which is typically used in audi-

[1] This research was supported by United States Public Health Service Grants MH-21934 and MH-07114, by National Science Foundation Grant GB-23685 and the State of Connecticut. Our thanks to Lee Schulhof for her assistance in data collection and analysis and to the Food and Drug Administration, Public Health Service, Psychotomimetic Agents Advisory Committee for supplying the LSD used in this study.

[2] Reprint requests should be sent to Michael Davis, Yale University School of Medicine, 34 Park Street, New Haven CT 06508.

tory experiments to mask extraneous sounds. Thereafter, the rate of subsequent response decrement of the LSD animals was indistinguishable from that of the saline animals. Based on these results it was concluded that LSD did not interfere with habituation but instead augmented the normal process of sensitization to background experimental conditions.

In a series of studies subsequent to that finding it was noticed, however, that LSD did not augment startle when tones were repeated at relatively short intervals even though it consistently did when tones were presented at relatively long intervals. This interaction between LSD and interval length suggested that LSD, in addition to influencing sensitization to background noise, might also alter processes that develop very rapidly after stimulus exposure.

To study processes that occur after a stimulus is presented, pairs of stimuli can be presented and sensory or motor evoked responses to each stimulus measured. When this is done, the size of the evoked response to the second stimulus is typically smaller, the shorter the interval between the two stimuli. Variously labelled the recovery process, temporal recovery process, recovery cycle, excitability cycle or pre-pulse inhibition, the basic phenomenon has been reported in a wide variety of experimental situations [2, 4, 6, 12, 14, 16, 18, 22, 24, 26, 28]. Cross modal temporal recovery effects, where presentation of a stimulus in one modality inhibits the response to a stimulus in another modality presented shortly thereafter also occur [12, 19, 25, 27]. Although similar to habituation in the sense that simple stimulus exposure results in subsequent response attenuation, the time course of this phenomenon is relatively short, on the order of msec or sec vs min, hr or even months for habituation (cf. [21]). In addition, direct experimental tests have been able to demonstrate the separate influences of pre-pulse inhibition and habituation using a variety of paradigms [7, 29].

To explain these findings it has generally been assumed that stimulus exposure, in addition to eliciting the measured response, also activates an inhibitory process which then decays over time. As the interval between the first and the second stimulus is increased, responsivity to the second stimulus increases because of the progressive decay of inhibition activated by the first stimulus. If LSD decreased stimulus-elicited inhibition or perhaps accelerated its rate of decay this should increase the subjective intensity of subsequent incoming stimulation and/or allow the reception of a greater number of sensory stimuli per unit time.

The acoustic startle reflex in the rat is a particularly sensitive index of the temporal recovery process. Startle amplitude can be inhibited by extraordinarily weak auditory pre-pulses [17] or relatively weak visual pre-pulses [19] over several msec or by the eliciting stimulus itself over several sec [7,29]. The purpose of the following series of experiments, therefore, was to evaluate whether LSD would alter the normal time course of the temporal recovery process using the acoustic startle reflex.

EXPERIMENT 1

The purpose of Experiment 1 was to evaluate whether the length of the interstimulus interval (ISI) does, in fact, make a difference as to whether or not a given dose of LSD will augment startle. To test this, rats were injected with LSD or saline and then presented with a series of tones at a long ISI followed by a series of tones at a short ISI followed by a series of tones at a long ISI. Only a single dose of 40 μg/kg was used since detailed dose response studies on the effects of LSD on startle are already available [9,23]. Testing was conducted over a period extending from 10 to 32 min after injection, which is a period of maximal LSD action on startle [9] for this dose.

Method

Animals. In this and all subsequent experiments the animals were experimentally naive male albino rats of the Sprague-Dawley strain that weighed between 300 and 350 g. Upon receipt from the supplier (Charles River Co.) the rats were housed in group cages of 4–5 rats each in a large colony room that was maintained on a 12:12 light-dark schedule. Food and water were continuously available.

Apparatus. Five separate stabilimeter devices were used to record the amplitude of the startle response. Each stabilimeter consisted of a 3.5 × 6 × 6 in. Plexiglas and wire mesh cage suspended with a 10 × 8 × 8 in. wooden frame. Within this frame the cage was sandwiched between 4 compression springs above, and a 2 × 2 in. rubber cylinder, below, with an accelerometer (M.B. Electronics Type 302) located between the bottom of the cage and the top of the rubber cylinder. Cage movement resulted in displacement of the accelerometer and the resultant voltage was fed through a matched accelerometer amplifier (M.B. Electronics Model N504), the output of which was proportionate to the velocity of accelerometer displacement.

The amplified signal was then fed to a specially designed sample and hold circuit. Basically this circuit consisted of 5 channels, 1 for each stabilimeter, and was used to sample the peak accelerometer voltage that occurred during a 200 msec time band immediately after the onset of the startle-eliciting stimulus. Immediately prior to this sample period, each channel was discharged so that any spontaneous activity occurring between stimulus exposures was erased. In this way the amplitude of the startle response of 5 rats was recorded simultaneously and stored in one of each of the 5 channels. Immediately after the sample period the output of each of the 5 channels was digitized through a specially designed analog to digital convertor and fed into a 14 channel Newport Printer. With 2 printing channels per cage, startle amplitude could vary from 0 to 99, allowing appreciable resolution among various startle amplitudes.

The 5 stabilimeters were located in an 8 × 8 × 7 foot dark, ventilated, sound attenuated chamber (Industrial Acoustic Co.). They were placed 45 in. from an Altec, high-frequency loud speaker, which was used to provide a 4000 Hz, 90 msec tone which was generated by a Hewlett Packard audio generator, amplified through an Altec 100 W power amplifier and shaped through a Grason-Stadler electronic switch to have a rise-decay time of 5 msec. Background white noise was provided by a Grason-Stadler white noise generator. The intensity of the tone (115 db) and the white noise (46 db) was measured with a General Radio Model 1551-C sound level meter (A scale) by placing the microphone in each cage and positioning the cages to have comparable readings.

Procedure. A total of 20 rats was used. On the first test day half the rats were injected intraperitoneally (IP) with 40 μg/kg LSD tartrate and half with an equivalent volume (1 cc) of 0.9 percent saline. Immediately after the injection the animals were placed in the startle test cages and 10 min later presented with 40 tones at a 15 sec ISI. Immediately

after this series the ISI was turned down to 2 sec and a total of 50 tones at a 2 sec ISI was presented followed immediately by a second series of 40 tones at a 15 sec ISI. Twenty-four hr later the same procedure was repeated except that rats that had previously been injected with LSD were now injected with saline and vice versa. Each animal thus served as his own control.

Results and Discussion

Figure 1 shows the mean amplitude startle response over blocks of 4 tones (i.e. 1 min periods) when the ISI was 15 sec and over blocks of 5 tones (i.e. 10 sec periods) when the ISI was 2 sec. The results were combined over the 2 test days since each day's results were similar and an analysis of variance using days, drugs and ISI as within animals factors combined over blocks of tones found no significant main effect of days nor any significant interactions involving days.

Figure 1 shows that LSD augmented startle when the ISI was 15 sec but not when it was 2 sec. That is, although there was no overall LSD-saline difference in startle, $F(1,19) = 3.72$, $p>0.10$, there was a highly significant Drug by ISI interaction. Augmentation of startle by LSD at the 15 sec ISI occurred both before ($t = 3.17$, $df = 19$, $p<0.02$) and after ($t = 2.64$, $df = 19$, $p<0.02$) the test period in which the ISI was 2 sec. The lack of difference at the 2 sec ISI cannot be attributed therefore to the effects of the drug having worn off at this time.

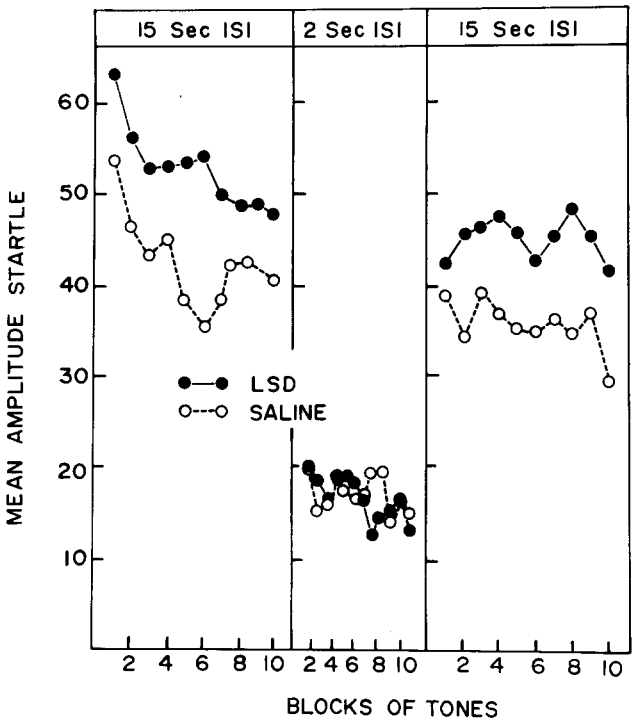

FIG. 1. Mean amplitude startle response over blocks of 4 tones (1 min periods) at the 15 sec ISI and over blocks of 5 tones (10 sec periods) at the 2 sec ISI following injections of saline or 40 μg/kg LSD.

Figure 1 also illustrates the different types of response decrement that can occur during repetitive stimulus exposure. First, was the general decrease in startle amplitude across blocks of tones at the 15 sec and 2 sec ISIs, $F(9,171) = 3.84$, $p<0.001$, as well as the decrease in startle from the first to the second series of 15 second tones, $F(1,19) = 16.81$, $p<0.001$. These decreases in startle indicate that habituation occurred under these conditions. Moreover, LSD did not appear to alter habituation, since neither the Drug by Blocks of Tones interaction nor the Drug by Test Period interaction approached statistical significance.

The other form of response decrement illustrated in Fig. 1 was the abrupt decrease in startle amplitude when the repetition rate was changed from 15 sec to 2 sec, $F(1,19) = 79.21$, $p<0.001$. This change in startle took place because less temporal recovery between successive tones could occur in the 2 sec condition, since the time since an immediately previous tone was always less in the 2 sec compared to the 15 sec condition. Viewed in this way, LSD appeared to interact with the temporal recovery process since it had no facilitatory effect on startle at the 2 sec ISI but only at the 15 sec ISI, $F(1,19) = 12.89$, $p<0.01$.

EXPERIMENT 2

The results of Experiment 1 suggest, therefore, that LSD might alter the temporal recovery process. More specifically, if the typical temporal recovery paradigm were used in which tones (pre-pulses) were presented at relatively long intervals followed by tones (test tones) at relatively short intervals, pre-pulse inhibition after LSD at short intervals (e.g. 2 sec) should be as great as that after saline, whereas pre-pulse inhibition at longer intervals (e.g. 15 sec) should be less after LSD. The purpose of Experiment 2 was to test this directly.

Method

A total of 20 rats was used. On the first test day half the rats were injected IP with LSD (40 μg/kg) and half with an equivalent volume of saline (1 cc). The animals were placed in the test cages and 32 sec later presented a total of 56 tones (pre-pulse). Each tone was followed either 2, 4, 8, or 16 sec later by a second tone (test tone). There were 14 occurrences of each of the 4 test intervals, distributed irregularly over the test session with the restriction that each interval had to occur once within every block of 4 successive intervals. The pre-pulse to pre-pulse interval varied from 34 to 48 sec while the test-tone to pre-pulse interval was constant at 32 sec. This test tone to pre-pulse interval was used since preliminary work showed recovery of startle amplitude under these conditions to be essentially complete by 32 sec. On the second test day all conditions were identical except that rats that had been injected with LSD were now injected with saline and vice-versa.

Results and Discussion

Figure 2 shows the mean amplitude startle response to the pre-pulse (P) and to the test tones at each of the various test-intervals, combined over trials and over days. Augmentation of startle by LSD was evident on pre-pulse trials and at all test intervals except the 2 sec interval. An overall analysis of variance found reliably higher startle amplitudes after LSD compared to saline, $F(1,19) = 13.18$, $p<0.005$, reliably greater startle, the longer the test interval, $F(4,76) = 146.93$, $p<0.001$, and a reliable drug by interval interaction, $F(4,76) = 17.31$, $p<0.001$. Subsequent individual comparisons using the method of Newman-Keuls

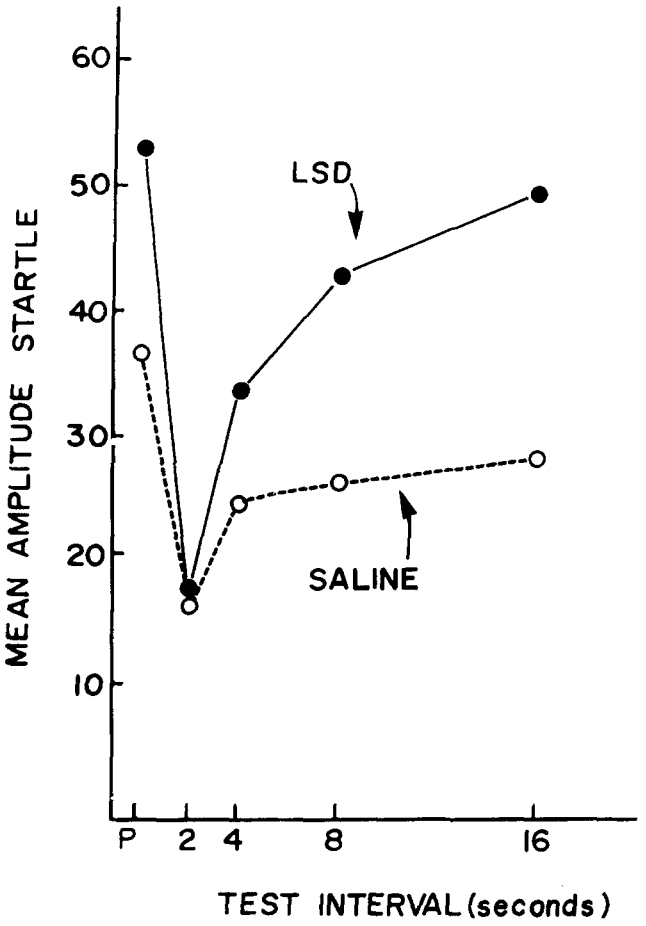

FIG. 2. Mean amplitude startle response to tones presented at various intervals after a pre-pulse tone following injections of saline or LSD.

[30] revealed significant augmentation of startle by LSD at every interval except 2 sec ($p<0.05$) or every interval except 2 and 4 sec ($p<0.01$).

In order to evaluate the time course of LSD's action on startle under these conditions, the mean startle amplitude at each of the 14 occurrences of the 4 test intervals and over the 4 pre-pulses during comparable periods were computed. These results are shown in Fig. 3. Similar to previous results [9] this dose of LSD began to increase startle within about 10 min after injection and continued to do so for most of the session. This was confirmed by a significant Drug by Blocks of Tones interaction, $F(13,260) = 3.10$, $p<0.01$. Most important, there was no augmentation of startle at the 2 sec test interval at any time, since there was no overall LSD augmentation of startle at the 2 sec ISI, $F(1,19) = 0.31$, $p>0.10$, nor any significant Drug by Blocks of Tones interaction within the 2 sec ISI condition, $F(13,260) = 0.19$, $p>0.10$.

EXPERIMENT 3

The lack of difference between saline and LSD at the 2 sec interval, in the face of significant augmentation at longer intervals, is critical to the conclusion that LSD affects the temporal recovery process rather than simply elevating overall startle amplitude. It is possible, however, that the lack of effect at the 2 sec ISI could have been caused by a floor effect. Thus LSD might augment startle at a 2 sec interval but this effect could have been masked because startle amplitude in the saline condition was at the bottom of the measurement system and/or at an insensitive point on the scale. To test this, it would be necessary to include some intervals shorter than 2 sec. If startle amplitude in the saline condition were lower than that measured at a 2 sec interval and yet LSD still did not augment startle at these short intervals this would show that the lack of difference at the 2 sec interval was not an artifact of a floor effect.

Method

A total of 20 rats were used. All conditions were identical to Experiment 2 except that test intervals of 0.5, 1, 2 and 16 sec were used.

Results and Discussion

Consistent with the earlier results, Fig. 4 shows that LSD and interval length interacted, $F(4,76) = 17.31$, $p<0.001$. Again LSD augmented startle on pre-pulse trials ($p<0.01$) and at the 16 sec interval ($p<0.01$), using the method of Newman-Keuls for multiple comparisons [30]. In addition, startle amplitude in the saline conditions at the 0.5 and 1 sec intervals was lower than it was at the 2 sec interval ($t = 5.43$ and 5.26, $p<0.001$). The lack of an LSD effect at the 2 sec interval cannot be attributed, therefore, to a floor effect and supports the conclusion that LSD does not decrease the inhibitory impact of pre-pulse stimulation but instead increases the rate of decay of that inhibition.

EXPERIMENT 4

Recently, considerable attention has been devoted to very short pre-pulse inhibitory effects which occur with startle [16,19]. By using a pre-pulse which itself does not elicit any measurable startle response, it can be shown that exposure to that pre-pulse still results in considerable inhibition of subsequent startle which is maximal in about 40–60 msec, decaying thereafter. Based on the results presented so far, one would expect that LSD would not augment startle over these short intervals. A direct test is necessary, however, since a different type of pre-pulse is required to explore these short intervals and LSD might act differently with this type of pre-pulse.

Method

The procedure was identical to that in Experiment 2 except that (a) test intervals of 2, 100, 2000 msec or 32 sec (no pre-pulse –NP) were used and (b) the pre-pulse was a 20 msec burst of 46 db white noise presented above a background noise of 28 db. The resting background noise of 28 was thus lower than the resting background noise of 46 db in the previous experiments.

Results and Discussion

Figure 5 shows the mean amplitude startle on the no pre-pulse trials and either 20, 100 or 2000 msec after the pre-pulse. No startle results are shown for the pre-pulse trials since, in this case, the pre-pulse did not elicit any

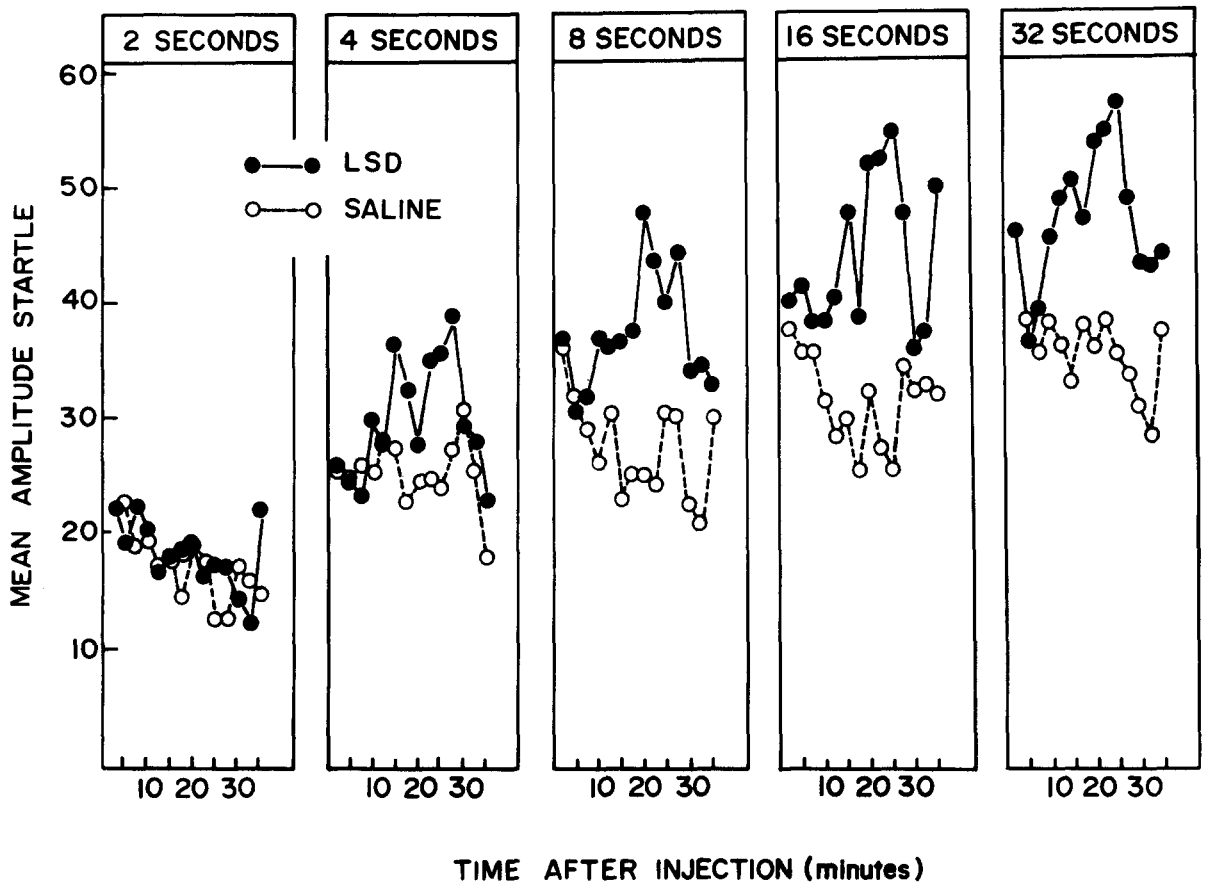

FIG. 3. Mean amplitude startle response for each occurrence of the test tones at the various test intervals (2, 4, 8 and 16 sec) and over blocks of 4 pre-pulses (32 sec) as a function of the time after injecting saline or LSD.

measurable startle. Figure 5 illustrates that pre-pulse inhibition grew from 20 to 100 msec, decaying thereafter, consistent with previous reports [16]. Most important, LSD did not augment startle at any of these intervals despite augmentation on the no pre-pulse trials. This was supported by an analysis of variance which showed no overall LSD effect but only a reliable interval effect, $F(3,51) = 37.72$, $p<0.001$, and a reliable drug by interval interaction, $F(3,51) = 3.99$, $p<0.02$, reflecting significant augmentation of startle only on the no pre-pulse trials ($t = 3.06$, $df = 19$, $p<0.01$). The fact that this latter difference, although significant statistically, was relatively small in comparison to the LSD-saline differences in the previous experiments at a 32 sec interval was most probably attributable to the lower level of noise that was used, since background noise interacts with LDS's effect on startle [9].

EXPERIMENT 5

Thus far it has been found that LSD augments startle when test intervals are longer than about 2 sec but not if they are shorter. In terms of the temporal recovery process the data suggest that stimulus exposure under LSD results in as much inhibition, but that LSD accelerates the subsequent rate of decay of that inhibition. The question still remains, however, as to whether this effect is specific to LSD or whether it also occurs when startle amplitude is augmented in other ways. One way to augment startle amplitude is simply to present a louder tone, since startle shows a strong dependence on stimulus intensity [10]. Another way is to use amphetamine, since startle amplitude is increased after d-amphetamine, provided the dose is high enough [5].

The purpose of the present experiment, therefore, was to compare the effect of these alternative ways of augmenting startle on the temporal recovery process with the previous data on LSD. The particular intensities and dose of amphetamine used were chosen so that all 3 ways of augmenting startle would produce roughly comparable augmentation at the longer test intervals, based on exploratory work. In this way the critical direct comparison between augmentation at long vs short intervals could be made across the various conditions.

Method

Two groups of 20 rats each were used. To measure temporal recovery each rat was presented with 60 tones (pre-pulse) followed either 0.5, 1, 2, 4, 8, or 16 sec later by a second tone (test-tone). There were 10 occurrences of each of the 6 test intervals distributed irregularly across the session with the restriction that each interval had to occur once within each block of 6 pre-pulses. For one group, half

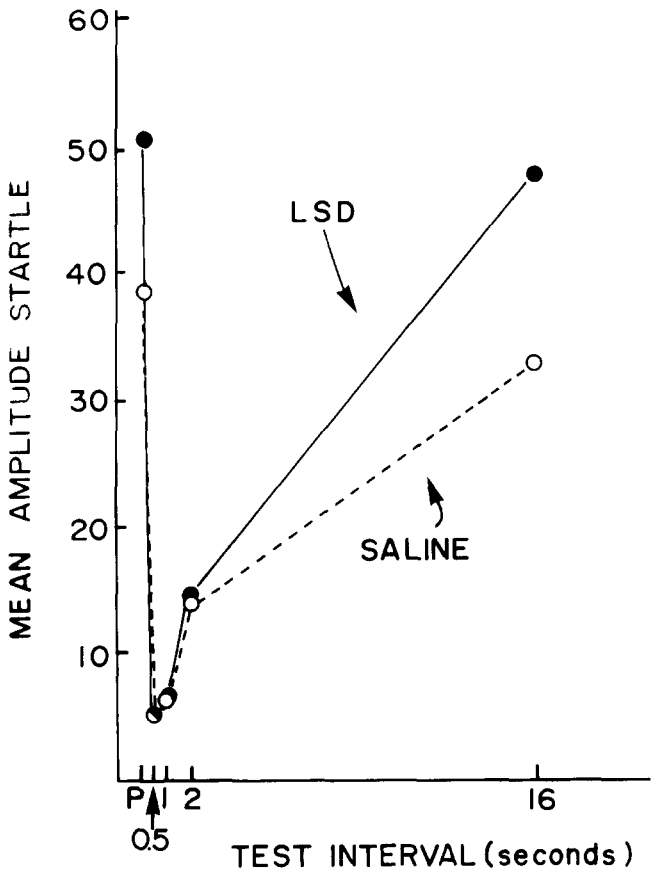

FIG. 4. Mean amplitude startle response to tones presented at various intervals after a pre-pulse tone following injection of saline or LSD.

the rats were injected IP with 8 mg/kg d-amphetamine sulfate and half with saline 5 min prior to testing and then retested 1 wk later under opposite drug conditions. For these animals the tone intensity was always 110 db. For the other group of rats, half were tested first with a 120 db tone and half with a 110 db tone with the reverse conditions the next day.

Results and Discussion

Figure 6 shows the mean amplitude startle response to the pre-pulse and at each of the 6 test intervals for the groups tested with amphetamine vs saline (upper panel) and 120 vs 110 db (middle panel). For comparative purposes the combined data from Experiments 2 and 3 using LSD vs saline is also shown (lower panel).

Figure 6 shows that both amphetamine or increasing the tone intensity were successful in augmenting startle and both of these effects were highly significant, $F(1,19) = 24.43$, $p<0.001$ and $F(1,19) = 68.40$, $p<0.001$, respectively. Temporal recovery was also evident, $F(6,114) = 56.46$, $p<0.001$ and $F(6,114) = 121.27$, $p<0.001$, respectively, and in both cases the 2 main effects interacted, $F(6,114) = 3.67$, $p<0.005$ and $F(6,114) = 21.82$, $p<0.001$, respectively. These interactions reflect the fact that the absolute size of the startle differences between amphetamine vs saline or 120 vs 110 db conditions were smaller, the shorter the test interval. Most important, however, was that despite being somewhat smaller, highly significant differences still existed at the short test intervals when the alternative methods of augmenting startle were used. Thus at the 2, 1 or 0.5 sec intervals startle amplitude was higher after amphetamine vs saline or with a 120 vs a 110 db tone (all p's<0.01 using the method of Newman-Kuels [30]).

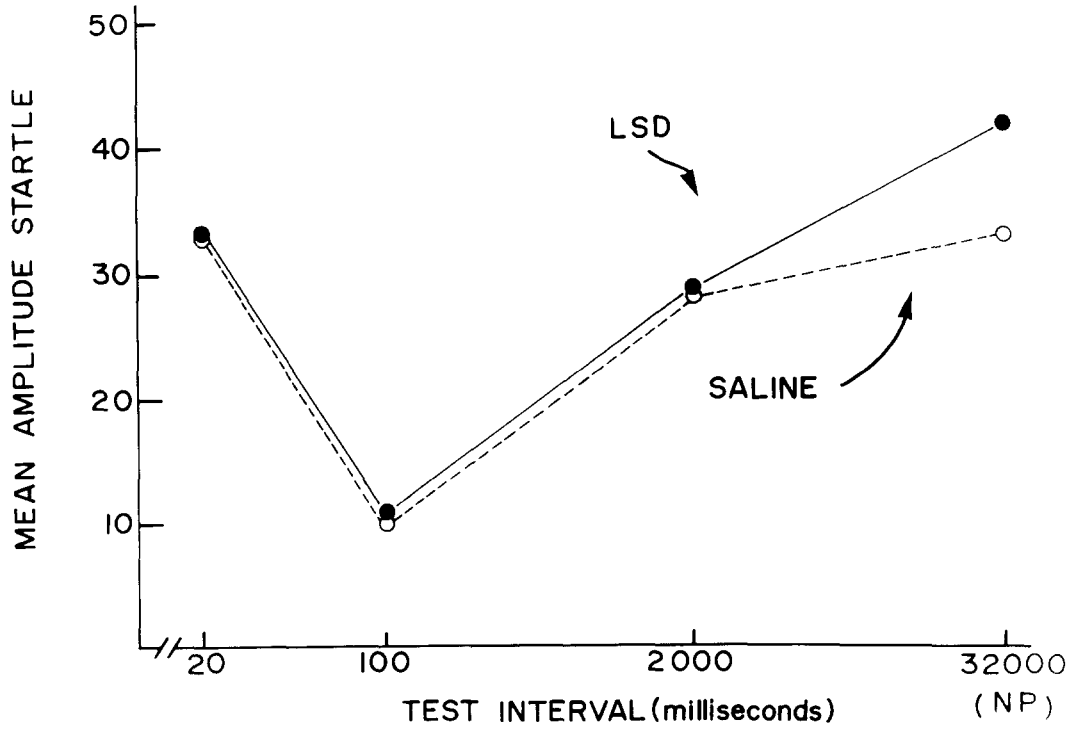

FIG. 5. Mean amplitude startle response to tones alone (NP) or to tones at various intervals (plotted on a log scale) after a 20 msec burst of white noise following injection of saline or LSD.

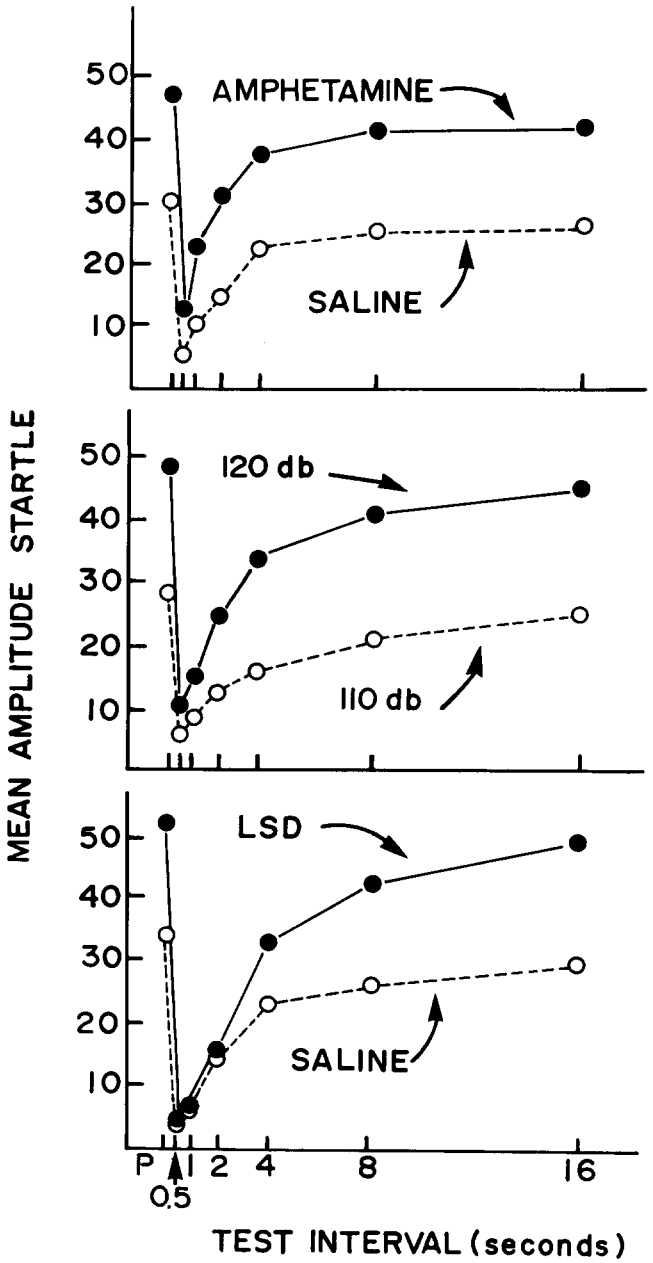

FIG. 6. Mean amplitude startle response to tones presented at various intervals after a pre-pulse tone following injection of saline vs. 8 mg/kg d-amphetamine (top panel) or saline vs. LSD (bottom panel) or when 120 db vs. 110 db tones were used (middle panel).

This is to be contrasted with LSD which did not augment startle at any of these intervals even though it did augment startle to a similar degree at longer intervals.

GENERAL DISCUSSION

The principal findings of the present study were that LSD augmented startle when long interstimulus intervals were employed but not when short test intervals were used. The critical interval was between 2 and 4 sec. The lack of difference at 2 sec was not caused by a floor effect since lower startle levels could still be detected at 1 or even 0.5 sec intervals. The effect was somewhat specific to LSD, since other ways of augmenting startle amplitude at long intervals to a level comparable to that produced by LSD resulted in a concomitant increase in startle amplitude at short intervals as well. Thus amphetamine or a higher tone intensity increased startle amplitude at all test intervals. In contrast, LSD did not seem to alter overall startle amplitude but instead appeared to alter the rate of temporal recovery.

One possible mechanism by which LSD might alter temporal recovery of the startle reflex would be to alter the time course of tone-elicited middle ear muscle contraction. It has been reported that lesions of the motor nuclei which control the middle ear muscles attenuate pre-pulse inhibition of the acoustic startle reflex using test intervals ranging from 1 to 16 sec [15]. Unfortunately, it is difficult to judge whether these lesions do in fact implicate the middle ear muscles in pre-pulse inhibition of startle, since the lesioned rats had grossly attenuated startle levels at all intervals. Floor effects or nonspecific effects attributable to sick animals might therefore have been operating. Nonetheless, it is interesting to note that when test-tone/pre-pulse ratios were computed in that experiment, pre-pulse inhibition still was evident in the lesioned rats at 1 and 2 sec intervals but not at the 4, 8 or 16 sec intervals. Since LSD also had different effects over these same sets of intervals in the present study, it is possible that LSD somehow altered the normal action on the middle ear muscles, maybe via the motor nuclei.

Another possibility would be to assume that temporal recovery effects are a form of short-term memory [7]. For example, information conveyed by the presentation of an auditory stimulus (the pre-pulse) might be transfered into some short-term memory system. If response to a stimulus was inhibited when the memory of that stimulus or its important attributes, such as abrupt onset, was well represented in short term memory, then response levels should be minimal shortly after a prior exposure to that stimulus but then increase as the information about that stimulus decayed from short-term memory. Using this model the conclusion would be that when relatively immediate tests of short-term memory are used (i.e. at short test intervals) LSD was ineffective, whereas when more remote tests (i.e. longer test intervals) are used, poorer recall after LSD was detected.

In the present context, this memory interpretation would predict that at very long test intervals or when animals were exposed to a loud tone for the very first time, LSD should not have any facilitatory effect. That is, once information had decayed completely from short-term memory (very long test intervals) or when nothing had ever been put into memory in the first place (a naive animal with respect to the tone) LSD should not augment startle if it were only influencing a memorial process. However, exploratory work using a 60 sec ISI or earlier work [9] in which response amplitude to the very first tone a rat had ever heard indicated that LSD still augmented startle under these conditions.

It may be, therefore, that LSD has several effects on startle. One would be to increase overall startle, (e.g. by increasing sensitization to noise) and the other to increase pre-pulse inhibition as well as to increase its rate of decay. At short test intervals response amplitude after LSD should

be higher by virtue of its overall effect on startle, yet lower by virtue of its effect of increasing pre-pulse inhibition. If these two opposing influences effectively cancelled each other out, no LSD-saline difference would be found over the short test intervals. At the long intervals, however, when pre-pulse inhibitory effects were now minimal, the effect of LSD on overall startle amplitude would be seen.

In fact, if the absolute decrease in pre-pulse to test-tone amplitude is used as a measure of pre-pulse inhibition, Figs. 2, 4, and 5 do indicate greater pre-pulse inhibition after LSD. Moreover, if the data in these figures are plotted in terms of test-tone/pre-pulse ratios, percent inhibition was greater for the LSD conditions at short intervals but less at the longer intervals, representing enhanced pre-pulse inhibition and accelerated recovery, respectively.

Enhanced pre-pulse inhibition by LSD might occur if LSD increased the apparent loudness of perhaps the "significance" of the pre-pulse [3] since louder pre-pulses result in greater subsequent inhibition [19]. Accelerated temporal recovery might occur if LSD inhibited mechanisms normally involved in the maintenance of stimulus-elicited inhibition. A principal mode of action of LSD is to inhibit unit firing of cells in the midbrain raphe nuclei [1] which themselves appear to inhibit the acoustic startle response [8]. Taken together, the various results suggest the midbrain raphe nuclei may be important in modulating startle and in maintaining pre-pulse inhibition and that LSD, by inhibiting this inhibitory mechanism, enhances startle along with accelerating the decay of pre-pulse inhibition.

REFERENCES

1. Aghajanian, G. K., W. E. Foote and M. H. Sheard. Action of psychotogenic drugs on single midbrain raphe neurons. *J. Pharmac. exp. Ther.* **171:** 178–187, 1970.
2. Allison, T. Recovery functions of somatosensory evoked responses in man. *Electroenceph. clin. Neurophysiol.* **14:** 331–343, 1961.
3. Bradley, P. B. and B. J. Key. The effect of drugs on arousal responses produced by electrical stimulation of the reticular formation of the brain. *Electroenceph. clin. Neurophysiol.* **10:** 97–110, 1958.
4. Chang, H. T. Changes in excitability of cerebral cortex following single electric shock applied to cortical surface. *J. Neurophysiol.* **14:** 95–111, 1951.
5. Cladel, C. E., M. H. Cho and R. D. McDonald. Effect of amphetamine and catecholamines on startle response and general motor activity of albino rats. *Nature* **210:** 864–865, 1966.
6. Clare, M. H. and G. H. Bishop. The intracortical excitability cycle following stimulation of the optic pathway of the cat. *Electroencephal. clin. Neurophysiol.* **4:** 311–320, 1952.
7. Davis, M. Effects of interstimulus interval length and variability on startle response habituation in the rat. *J. comp. physiol. Psychol.* **72:** 177–192, 1970.
8. Davis, M. and M. H. Sheard. Habituation and sensitization of the rat startle response: Effects of raphe lesions. *Physiol. Behav.* **12:** 425–431, 1974.
9. Davis, M. and M. H. Sheard. Effects of lysergic acid diethylamide (LSD) on habituation and sensitization of the startle response in the rat. *Pharmac. Biochem. Behav.* **2:** 675–683, 1974.
10. Davis, M. and A. R. Wagner. Startle responsiveness after habituation to different intensities of tone. *Psychonom. Sci.* **12:** 337–338, 1968.
11. Dodge, R. and C. M. Louttit. Modification of the pattern of the guinea pig's reflex response to noise. *J. comp. Psychol.* **3:** 267–285, 1926.
12. Dubner, R. and L. T. Rutledge. Intracellular recording of the convergence of input upon neurons in cat association cortex. *Expl. Neurol.* **12:** 349–369, 1965.
13. Freedman, D. X. The psychopharmacology of hallucinogenic drugs. *A. Rev. Med.* **20:** 409–418, 1969.
14. Grings, W. W. and A. M. Schell. Magnitude of electrodermal response to a standard stimulus as a function of intensity and proximity of a prior stimulus. *J. comp. physiol. Psychol.* **67:** 77–82, 1969.
15. Groves, P. M., R. D. Boyle, R. L. Welker and S. W. Miller. On the mechanism of pre-pulse inhibition. *Physiol. Behav.* **12:** 367–375, 1974.
16. Hoffman, H. S. and J. L. Searle. Acoustic and temporal factors in the evocation of startle. *J. acoust. Soc. Am.* **43:** 269–282, 1968.
17. Hoffman, H. S. and B. L. Wible. Role of weak signals in acoustic startle. *J. acoust. Soc. Am.* **47:** 489–497, 1970.
18. Hughes, J. and H. S. Gasser. The response of the spinal cord to two afferent volleys. *Am. J. Physiol.* **108:** 307–321, 1934.
19. Ison, J. R. and G. R. Hammond. Modification of the startle reflex in the rat by changes in the auditory and visual environments. *J. comp. physiol. Psychol.* **75:** 435–452, 1971.
20. Key, B. J. and P. B. Bradley. The effects of drugs on conditioning and habituation to arousal stimuli in animals. *Psychopharmacologia,* **1:** 450–462, 1970.
21. Leaton, R. N. Long term retention of the habituation of lick suppression in rats. *J. comp. physiol. Psychol.* **187:** 1157–1164, 1974.
22. Marshall, W. H. Excitability cycle and interaction in geniculate-striate system of cat. *J. Neurophysiol.* **12:** 277–288, 1949.
23. Miliaressis, T. E. and J. St-Laurent. Effects of de l'amide de l'acid lysergigne -25 sur la reaction de sursant chez le rat. *Can. J. Physiol. Pharmac.* **52:** 126–129, 1974.
24. Rosenzweig, M. R. and W. A. Rosenblith. Responses to successive auditory stimuli at the cochlea and at the auditory cortex. *Psychol. Monogr.* **67:** 1–26, 1953.
25. Schneider, A. S. and J. L. Davis. Interactions of the evoked responses to visual, somatic, and auditory stimuli in polysensory areas of the cat cortex. *Physiol. Behav.* **13:** 365–372, 1974.
26. Shagass, C., M. Schwartz and K. Krishnamoorti. Some psychological correlates of cerebral responses evoked by light flash. *Psychosom. Res.* **9:** 222–231, 1965.
27. Thompson, R. F., H. E. Smith and D. Bliss. Auditory, somatic sensory and visual response interactions in association and primary cortical fields of the cat. *J. Neurophysiol.* **26:** 365–378, 1963.
28. Westecker, M. E. Time course of facilitation and inhibition in the olfactory bulb investigated with double pulse stimulation of the lateral olfactory tract. *Brain Res.* **16:** 527–529, 1969.
29. Wilson, J. and P. M. Groves. Refractory period and habituation of acoustic startle response in rats. *J. comp. physiol. Psychol.* **83:** 493–498, 1973.
30. Winer, B. J. *Statistical Principles in Experimental Design.* New York: McGraw Hill Book Co., 1962.