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The Lack of Effect of LSD 25 on Amygdaloid and Cortical Attention Responses*

By

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With 3 Figures in the Text

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Introduction

While there is now reason to question the suggested similarity between the behavioral effects of d-lysergic acid diethylamide (LSD 25) and certain of the symptoms of schizophrenia (DENBER 1957; LINDEMANN and FELSINGER 1961), there is, nevertheless, a continuing research interest in the psychopharmacological properties of LSD 25. There seems little doubt that knowledge of the site of action and mechanism of action of this potent psychotropic drug would contribute meaningfully to our understanding of central nervous system function.

Perhaps the most striking psychological effect of LSD 25 is the alteration in perceptual processes reported alike both by experimental subjects and clinical patients (STOLL 1947; BERCEL et al. 1956; ROTHLIN 1957; CARLSON 1958). Further, there are often complaints of an inability to concentrate or maintain a fixed attention to some on-going environmental event. The heightened distractability with irrelevant shifts in attention may be induced by even minimal extraneous sounds (CARLSON 1958).

Such findings strongly suggested that one of the effects of LSD 25 might be a depression of the arousal threshold and, indeed, BRADLEY and KEY (1958), working with cats, have demonstrated this. Following administration of LSD 25, there is a lowered threshold for arousal as measured both by EEG and behavioral indices. These workers find that it is the threshold for arousal from peripheral sensory stimulation

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that is reduced while there is no effect on the arousal threshold as induced by direct stimulation of the reticular formation. Their general conclusion is that the effect of LSD 25 is closely related to the incoming influences from the environment.

These same workers also studied EEG and behavioral arousal following both peripheral and reticular stimulation in cats that were treated with chlorpromazine. As in the case of LSD 25, they observed that chlorpromazine markedly influenced peripherally induced arousal while having little effect on arousal induced by direct stimulation of the brainstem reticular formation. Further, the effect of chlorpromazine (contrary to LSD 25) was to elevate the arousal threshold. This contrasting effect of the two drugs is of interest in view of the successful clinical use of chlorpromazine as an antagonist to LSD 25 (see: COHEN 1960). From these combined findings, BRADLEY and KEY concluded that chlorpromazine and LSD 25 had entirely opposite effects on the sensory influences reaching the reticular system.

Further information on the site of action of the chlorpromazine effect on arousal is supplied by KAADA and BRULAND (1960). These workers studied the effect of chlorpromazine on the "attention" response which can be elicited by electrical stimulation of certain cortical areas, the amygdaloid complex, the thalamic intralaminar nuclei and the mesencephalic reticular formation. This response seems similar to the behavioral arousal described by BRADLEY and KEY. Previous work at the University of Oslo has already shown that EEG arousal can be obtained from the same electrode sites yielding attention responses (FANGEL and KAADA 1960; KAADA and JOHANNESSEN 1960; URSIN and KAADA 1960a).

In the first place, KAADA and BRULAND confirmed the finding of BRADLEY and KEY to the effect that chlorpromazine has little or no depressant effect on the attention response induced by stimulation of the brainstem reticular formation. On the other hand, chlorpromazine blocked the attention response elicited from the responsive cortical areas. Higher doses similarly depressed the attention response produced by stimulation of the amygdala and intralaminar nuclei of the thalamus. It is believed that the attention response elicited from these areas is mediated through the brain stem reticular formation (JANSEN, ANDERSEN and KAADA 1955/56; URSIN and KAADA 1960b). BRODAL (1957) has already pointed out, on the basis of morphological studies, that the reticular formation may be divided into a lateral portion concerned with "receptive" and "associative" processes and a medial portion concerned with "effector" processes. KAADA and BRULAND therefore suggested, that the depressant effect of chlorpromazine on these responses was probably mediated through an alteration in the receptive elements in the lateral part of the reticular formation.

The present report deals mainly with the effects of LSD 25 on the threshold for the attention response elicited by stimulation of the cerebral cortex, the amygdaloid nuclear complex and the brain stem reticular formation. In addition, a few observations were made following stimulation of intralaminar thalamic nuclei, caudate nucleus and septal area. These experiments were undertaken to determine whether the threshold for such centrally induced responses is lowered by LSD 25 in a manner comparable to the drug effect on peripherally induced arousal. It was hoped that the findings would help shed further light on the question of whether LSD 25 and chlorpromazine have similar sites of action.

Material and Methods

Ten adult cats were used. 5 or 6 bipolar, needle electrodes were implanted in each animal through small burr holes in the skull. The cats were operated during pentobarbital (Nembutal) anesthesia. The electrodes, insulated except for the tips, were implanted in the following structures; the mesencephalic reticular formation, the amygdaloid nuclear complex, temporal cortex (lower portion of the posterior ecto- and suprasylvian gyri), intralaminar thalamic nuclei, caudate nucleus and septal area. The technique employed for the implantation is similar to the one used by KAADA and BRULAND (1960).

Two to four days post-operatively the freely moving, unanesthetized cats were stimulated through the implanted electrodes using monophasic, square-wave pulses of 8 msec. duration and a frequency of 40 c.p.s. for 10 seconds. The stimulus intensity was gradually increased, always starting with subthreshold values. The threshold of the behavioral attention response was determined for each site yielding this response. The threshold was checked from day to day. If spontaneous variations were found to exceed 0.5 volts, the data from that placement were not included in this report.

The voltages used ranged from 0.5 to 4.0 volts (see Figs. 1—3). The important thing was felt to be threshold variations in the individual electrodes. The absolute values were not regarded as important and must be looked upon as being somewhat arbitrary. New electrodes were made for each experiment and their resistance varied from 10000 to 40000 ohms. After the termination of the experiment, it became evident that the readings of the voltage output of the stimulator, used in cats 1—6, were falsely low. (It was not possible to determine the true voltage levels by recalibration since the equipment had been overhauled before this particular error was noted.) It is for this reason that the thresholds for the first 6 cats are lower than for subsequent animals.

Small ampules of LSD 25 (Delysid) were used, each containing 100 μg, a new ampule being opened for each experiment. The drug was administrated either intraperitoneally or intravenously through a

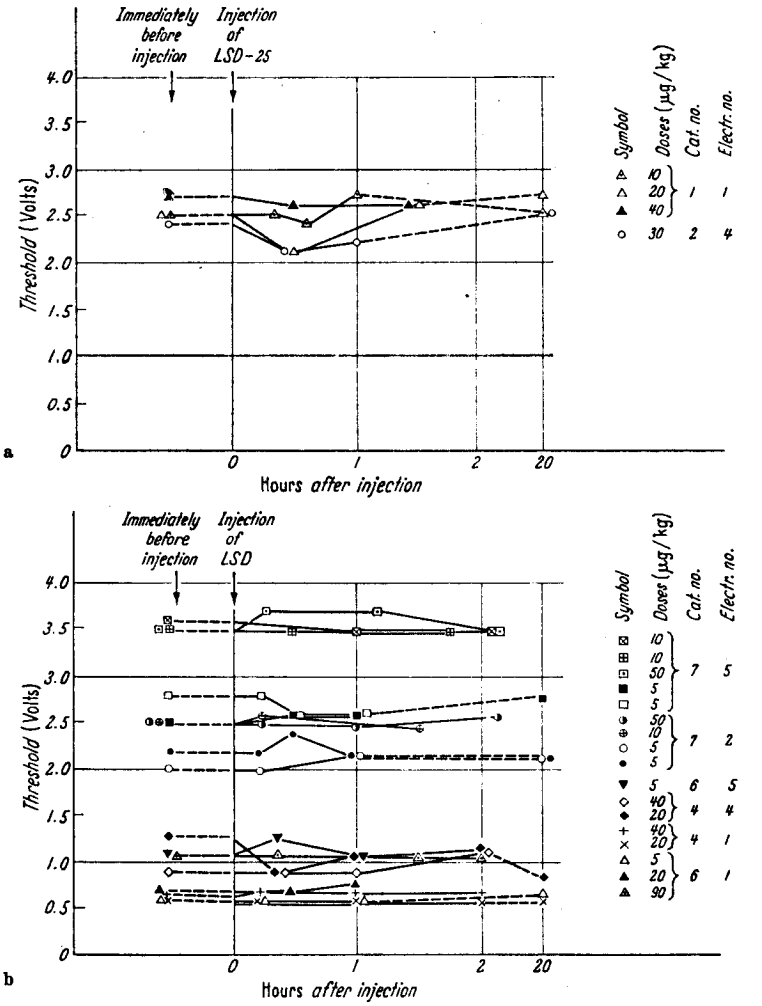

Fig. 1a and b. Stimulation in brain stem reticular formation. Thresholds for attention responses before, during, and after LSD 25 treatment. Doses and symbol for each trial are indicated in the column on the right side. a intraperitoneal injections; b intravenous injections

polyethylene catheter chronically implanted in the external jugular vein. The doses ranged from 5—200 μg/kg, but were usually 10—50 μg/kg.

The response threshold values were systematically tested immediately before the injection of the drug, and then retested 2 to 4 times

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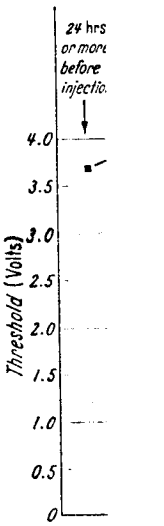

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One series of threshold determinations for a particular electrode (before, during and after treatment with LSD 25) is referred to in the text and figures as one trial. A number of such trials were run for most electrode placements at various dosage levels. No drug trial was ever run, however, less than 24 hours after a previous trial, an inter-trial

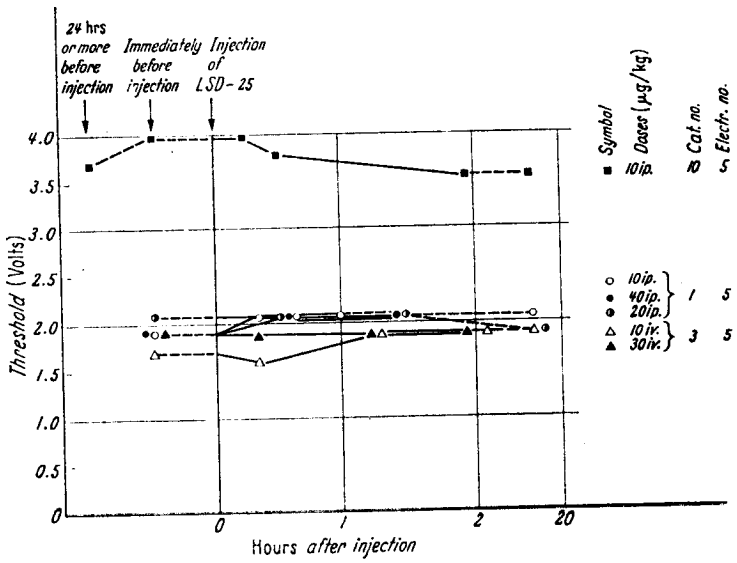

Fig. 2. Stimulation in temporal cortex. Thresholds before, during, and after LSD 25 treatment for attention responses yielded from lower portion of the posterior ecto- and suprasylvian gyri. Doses and symbol for each trial are indicated in the column on the right side. All injections in these trials were given intravenously

interval that was felt to be safe in view of the 130 minute biological halflife reported for LSD 25 in cats (AXELROD et al. 1957).

All cats were not tested the same number of times, nor were all electrodes in a particular cat given a uniform number of trials. This lack of uniformity was necessitated by the fact that certain electrodes did not remain functional throughout the entire experiment and certain stimulation sites were too variable to be used (as described above). Electrodes from which no attention response was elicited are, of course, not included in this present report.

At the termination of the experiments, all electrode placements were identified histologically. In the mesencephalic reticular formation, 8 electrodes, yielding the attention response, were tested. The total number of trials for these 8 placements was 21 (Fig. 1a, b). For the

amygdala there were 9 electrodes, 16 trials (Fig. 3a, b); temporal cortex: 3 electrodes, 6 trials (Fig. 2); intralaminar thalamic nuclei: 2 electrodes,

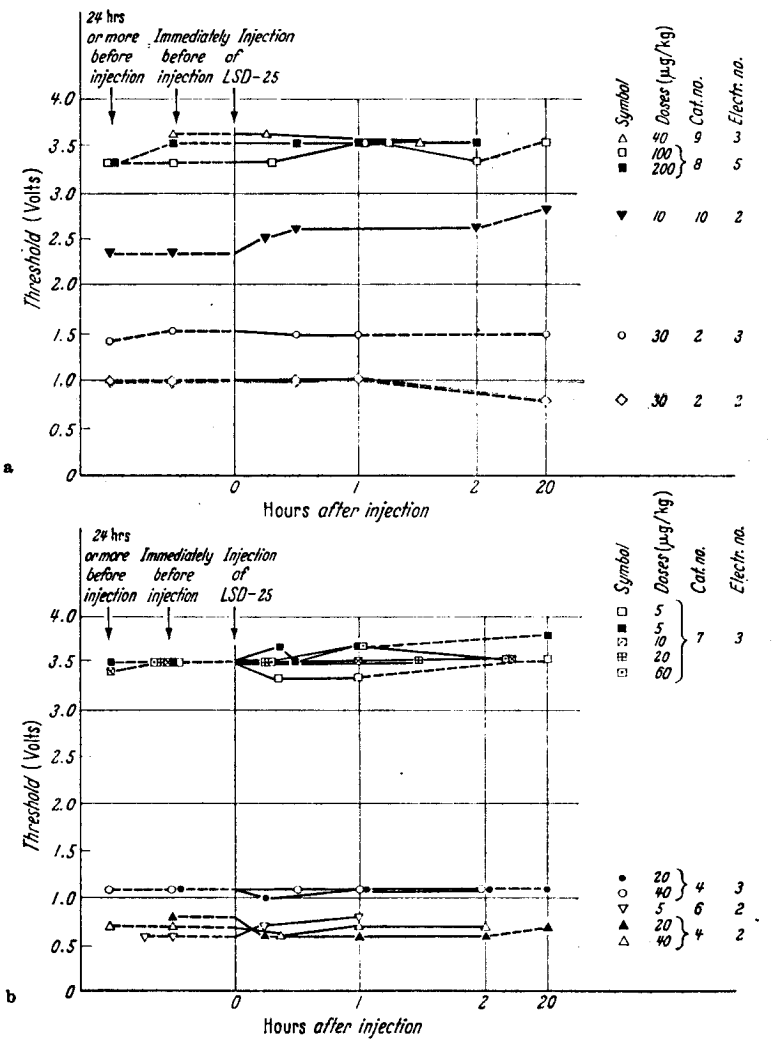

Fig. 3 a and b. Stimulation in amygdala. Thresholds for attention responses before, during, and after LSD 25 treatment. Doses and symbol for each trial are indicated in the column on the right side. a intraperitoneal injections; b intravenous injections

2 trials; caudate nucleus 2 electrodes, 2 trials; septal area 2 electrodes, 2 trials.

Care was taken never to stimulate any point more than a few times above threshold values in order to avoid any possible habituation.

Results

General behavioral changes. The general behavioral changes following injections of LSD 25 were not dramatic. Sometimes, the cats were definitely more alert than normal cats, although the reasons for this alertness were not always apparent. Sometimes it seemed clear that a cat was reacting very strongly to slight noises or movements in the environment, but at other times the observer could find no reason for the arousal. The experiments were not undertaken in a soundproof room, therefore, the cats may have reacted to some stimulus unnoticed by the observer. During these episodes of arousal the cats occasionally grasped in the empty air in front of themselves as if trying to hit something ("catching flies").

Most of the time, however, the cats did not seem to be unusually alert. On the contrary, the cats would commonly withdraw, lie down, and half-close their eyes—having the appearance of a drowsy or sick animal. In these periods, even very strong noises often did not yield any behavioral response at all. When the highest doses (50—200 μg/kg) were given, a slight ataxia developed.

"Attention response" thresholds. The characteristics of the attention response are: opening of the eyes, retraction of the nictitating membrane, arrest of ongoing activity, pupillary dilatation, raising of the head, and searching movements of the head to the side opposite that stimulated. The same behavior changes are also seen in normal cats during orienting behavior, PAVLOV's "orienting reflex" (see FANGEL and KAADA 1960), as well as during the occasional periods of alertness seen in the LSD 25-treated cats.

The criteria in this study for the threshold of this response during stimulation were: opening of the eyes, retraction of the nictitating membrane, and slight pupillary dilatation. The other behavioral characteristics of the attention response are seen when the stimulus intensity is increased slightly above threshold value. The arrest response could not be used as a threshold criterion since the cats usually were inactive following treatment with LSD 25. The brain stimulation was always carried out against a behavioral background of inactivity and quietness, althoug no animal was ever asleep.

It is evident from Figs. 1—3 that there were no significant alterations in the threshold of the behavioral attention responses following any of the doses of LSD 25. This was found to be true for the responses elicited from stimulation of the mesencephalic reticular system, the amygdaloid nuclear complex and the temporal cortex as well as from the other structures where only a few electrodes were placed. There was no difference in response threshold with either intraperitoneal or intravenous injections of the drug. A few of the electrodes were also tested

for the effect of chlorpromazine. The data obtained confirmed the results reported by KAADA and BRULAND. It was thus demonstrated that, while chlorpromazine produced an increased threshold for attention responses evoked from cortex and amygdala, LSD 25 had no effect on these responses.

Discussion

General behavior. Most papers dealing with general behavioral patterns after intraperitoneal or intravenous injections of LSD 25, stress the alerting effects of the drug (APTER 1957; BRADLEY and ELKES 1957; MONNIER 1957; BISHOP et al. 1958). In addition to alertness, HALEY and DASGUPTA (1958) report that LSD 25 produced "signs of fear" in their experimental cats. None of the treated cats observed in the present experiments showed any of the behavioral patterns which are ordinarilly interpreted as "fear" or "flight" (For example, see URSIN and KAADA 1960a; URSIN 1960). The absence of this particular drug effect is also confirmed in ongoing experiments utilizing a more objective behavioral rating technique.

Spontaneous alerting and orienting behavior were seen only occasionally following treatment with LSD 25. These short episodes sometimes were subsequent to obvious extraneous noises, but, at other times, the cause of the alertness was not obvious to the observer. Such periodic arousal might have been due to the lowered threshold for auditory stimuli, as has already been reported by BRADLEY and KEY (1958). In humans, a periodicity in the subjective experience induced by LSD 25 has been reported by SANDISON et al. (1954) and SCHWARZ et al. (1956).

The long periods of sedation seen in the present treated cats have not been dealt with in detail by other authors. However, KEY and BRADLEY (1960) reported that even if their cats became noticeably more responsive to external stimuli following injection of LSD 25, they could usually be induced to sleep provided all ambient sensory stimulation was reduced to a minimum. In the present experiments, all extraneous noises were routinely reduced as much as possible and even if the cats were not induced to sleep their inactivity was very striking. Thus, LSD 25 may have a sedative effect on cats in the absence of sufficient environmental stimulation. However, humans under influence of LSD 25 often complain of feelings of illness or nausea (STOLL 1947; SANDISON et al. 1954; BERCEL et al. 1956; COHEN 1960). It seems more likely therefore that the inactivity seen in the cats is simply the result of such feelings of sickness or bizarre sensory effects.

Attention response following stimulation. The present results confirm the findings of BRADLEY and KEY (1958) to the effect that LSD 25 has no effect on the threshold of the attention response when the response

is induced by stimulation of the mesencephalic reticular formation. Further, there is no drug effect on the attention response threshold when the stimulating electrode is situated in temporal neo-cortex, or amygdala, or in any of the other central nervous system structures studied in the present work. It has already been shown by BRADLEY and KEY (1958) that at least with an appropriate drug (amphetamine), it is possible to lower arousal thresholds associated with reticular stimulation.

The experiments in the present paper were undertaken in order to establish the effect of LSD 25 on the threshold for the behavioral attention response elicited by electrical stimulation of the "telencephalic attention areas" (amygdala and the responsive cortical areas). KAADA and BRULAND (1960) demonstrated that such thresholds were increased following injections of chlorpromazine. BRADLEY and KEY (1958) forwarded the hypothesis that LSD 25 and chlorpromazine had entirely opposite effects on sensory influences in the reticular formation mediated via the collaterals from the afferent pathways. With regard to the effect of chlorpromazine, KAADA and BRULAND suggested that the effect was due to a blocking of neurones in the reticular system receiving impulses both from the sensory pathways and the telencephalic attention areas. Descending impulses from the cortical fields in question are known to some extent to converge on the same brain stem reticular neurones as receive sensory information (BAUMGARTEN et al. 1954; SCHEIBEL et al. 1955; HERNÁNDEZ-PÉON and HAGBARTH 1955; FRENCH et al. 1955).

If the "site of action" of chlorpromazine is as outlined above, LSD 25 cannot be acting on the same neural mechanisms" in an entirely opposite way" as suggested by BRADLEY and KEY since the present results show that there is no effect of LSD 25 on the telencephalic attention response. On the other hand, LSD 25 and chlorpromazine may both be acting on the neurones in the reticular formation that receive collaterals from the sensory pathways if these reticular cells are, in fact, separated from those that receive impulses from telencephalic attention areas.

In other words, if the reticular formation reception of afferent collaterals and descending fibers from telencephalic attention areas are actually handled by two different parts of the reticular formation, the peripheral sensory portion could be open to influence by both chlorpromazine and LSD 25, while the telencephalic reception area would apparently be influenced only by chlorpromazine.

If the telencephalic attention areas, however, project to the same neurones in the reticular system as the fibers responsible for the peripherally induced arousal, another explanation must be offered for the site of action of LSD 25. The drug may then be acting directly on the

sense organs, or interfering with the central nervous control of the sensory pathways, thus affecting the filtering and selecting mechanisms of the afferent systems (For a review, see LIVINGSTON 1960). The site of action for such a centrifugal mechanism would probably also be the reticular system, but not on the "input" side as earlier suggested. KEY and BRADLEY (1960), however, find it unlikely that the action of LSD 25 is on the afferent pathway itself, since the threshold for click responses recorded from the auditory cortex is unaltered.

Whether the effect of LSD 25 is on the peripheral sense organs or on the afferent pathway or in the reticular system, the effect on the filtering and integration of the impulses from the peripheral sense organs seem to be of decisive importance for the total effect of the drug. If this is the case, the psychological effects could, at least to some degree, be secondary to the altered perception and body image. This might offer an explanation for the great variance in symptoms and the important influence on the symptoms of the "premorbid" personality type described in experiments with humans (SANDISON et al. 1954; BERCEL et al. 1956; DENBER 1957; ROTHLIN 1957; COHEN 1960).

LSD 25 does not seem to affect the various sense organs in the same way. There is evidence for an increased threshold for visual stimuli in man (CARLSON 1958) and pigeons (BLOUGH 1957). The accuracy in a visual discrimination test in pigeons was improved, and there was a slight improvement for the delayed discrimination test. The lowering of the threshold for arousal produced by auditory stimuli reported by BRADLEY and KEY was further studied by KEY and BRADLEY (1960). They found LSD 25 to lower the threshold for arousal by auditory stimulation to a level probably near the threshold for hearing in the cat.

It is relevant to this problem that LSD 25 was found to reduce the reaction time for a conditioned flight response in rats and tests of analgesia in the mice (TAESCHLER et al. 1960). The effect was regarded as the result of sensitization of central nervous structures to afferent impulses. Further, in psychological testing of humans under the influence of LSD 25, EDWARDS and COHEN (1961) found evidence for a damping of somaesthetic sensations, and a reduction in visual cues. The authors analysis of the results did not support an interpretation based on an "impairment of attention".

Electrophysiological studies have brought forward evidence for a direct influence of LSD 25 on the cerebral cortex. An inhibitory effect has been demonstrated on the evoked potentials in the cerebral cortex in cats and humans (GRENELL 1957; MARRAZZI 1957; PURPURA 1957). PURPURA postulated this to be due to an inhibitory action on cortical dendritic activity.

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Other electrophysiological data support the idea of LSD 25 having mainly a peripheral site of action. APTER (1957) reports that the spontaneous activity of the visual system initiated by LSD 25 starts in the retina itself. The activity is facilitated at each synapse with the maximum activity being in the cortex. The activity in the cortex cannot appear unless the connection with the retina is intact.

Important evidence against the assumption of LSD 25 acting mainly on the cerebral cortex has been brought forward by NEUHOLD et al. (1957). They have shown that excitation and increased body temperature following LSD 25 in rabbits are unchanged in decorticated animals. They conclude that an essential cortical site of action of LSD 25 regarding these effects can be excluded.

Apparently, there is no simple generalization available to account for all these results. The only common factors appear to be that the afferent impulses are variously affected by the drug, and that this seems to be a basic mechanism for the effect of LSD 25 on the central nervous system. This assumption is most in line with the results of BRADLEY and KEY and those presented in this paper showing that attention or arousal induced by peripheral stimuli is affected by the drug, while similar responses elicited by central nervous system stimulation is not.

Alterations in consciousness and emotionality during temporal lobe seizures are believed to be due to interference with the temporal lobe structures yielding attention responses and emotional behavior on stimulation (KAADA 1960; URSIN and KAADA 1960a; URSIN 1960). The ineffectiveness of LSD 25 in altering the threshold for the attention response elicited from the amygdaloid nuclear complex and other parts of the temporal lobe may have some bearing on the finding that LSD 25 does not activate temporal lobe epilepsy (SCHWARZ et al. 1956). Instead of provoking epileptic attacks, LSD 25 has been shown to inhibit the spread and occurence of strychnine-induced convulsive discharge in the electroencephalogram of rabbits (WINKEL 1958).

Summary

1. The behavioral attention response (behavioral arousal associated with contralateral searching movements) was induced in cats by stimulation of the temporal lobe neocortex, the amygdaloid nuclear complex, and the mesencephalic reticular formation. The threshold of the attention responses was tested before and after intravenous or intraperitoneal injection of LSD 25. The threshold was found to be unaltered by the drug for all central nervous system structures studied.

2. Since there was no effect of LSD 25 on the telencephalically induced attention response while chlorpromazine has a clear blocking effect under the same experimental circumstances, it seems no longer correct

to consider these two psychotropic drugs as having any simple opposite effect on nervous system function.

3. The results are believed to have some bearing upon the possibility that the main effect of LSD 25 is due to interference with sensory inflow to the central nervous system.

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