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Differential Effects of LSD Serotonin and *l*-Tryptophan on Visually Evoked Responses

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STRAHLENDORF, J. C. R., F. J. GOLDSTEIN, G. V. ROSSI AND R. T. MALSEED. *Differential effects of LSD, serotonin and l-tryptophan on visually evoked responses.* PHARMAC. BIOCHEM. BEHAV. 16(1) 51–55, 1982.—Alterations in photically-evoked cortical responses were assessed in immobilized artificially respired cats following intraraphe microinjections of LSD and serotonin (5-HT) and IV administration of LSD and *l*-tryptophan. Both systemic (10–100 μg/kg; N=5) and intraraphe (0.25 μg; N=10) LSD significantly increased the amplitudes of the three primary components of the visual evoked response (VER). In contrast, the same VER components were significantly depressed following intraraphe 5-HT (30 μg; N=4) and IV *l*-tryptophan (100 mg/kg; N=6), a serotonin precursor that elevates raphe 5-HT levels. Intraraphe cinanserin (180 μg; 30 minute pretreatment) completely reversed LSD-induced enhancements in all three components ($p<0.01$). Depressions of VER following intraraphe 5-HT (30 μg) were also antagonized by cinanserin, although to a lesser degree ($p<0.05$ for first 2 components only) than with LSD. The depressive effects of *l*-tryptophan (100 mg/kg) were unaffected by cinanserin. Modification of raphe neuronal activity can significantly alter photically evoked responses, and may explain the perceptual disturbances associated with LSD, i.e., depression of an area (raphe) normally inhibiting forebrain areas of the visual system.

Visual evoked cortical response *l*-Tryptophan Cats Cinanserin Lysergic acid diethylamide (LSD) Raphe nucleus Serotonin (5-HT) Disinhibition Visual hallucinations

LYSERGIC Acid Diethylamide (LSD) is a potent psychoactive agent capable of eliciting profound perceptual distortion, including visual hallucinations. Systemic administration of LSD in several species, including man, has resulted in either facilitation or depression of the visual evoked response (VER) depending upon dosage and route of administration, although low doses commonly elicited an enhanced photically evoked response (see [11]). Behavioral studies have suggested that serotonergic mechanisms may play a role in perceptual modification induced by LSD [18, 26, 27]. Serotonin (5-HT) cell bodies have been detected in the dorsal raphe nucleus, axons of which innervate many forebrain areas, including the superior colliculus and lateral geniculate bodies, important areas for visual activity [10,16]. Moreover, the dorsal raphe, via serotonergic pathways, appears to exert a uniformly inhibitory synaptic action in the forebrain [2,7]; thus, an important role of serotonergic raphe neurons may be to dampen overreactiveness to visual as well as various other stimuli.

Electrical stimulation of the midbrain raphe has been shown to increase regional turnover of 5-HT [22] and to decrease amplitudes of peripherally evoked cortical responses [21]. In contrast, LSD has been reported to reduce brain 5-HT turnover [20] and reversibly inhibit raphe neuronal firing following both systemic [1,26] and microiontophoretic [17] application. Reduction of raphe-mediated forebrain inhibition via LSD-induced depression of raphe activity could result in disinhibition of raphe target neurons (e.g., nuclei of the visual system), thereby increasing activity in the primary visual pathway. The altered perceptual phenomena associated with LSD may therefore be related to its ability to compromise the tonic inhibitory control exerted by the raphe on forebrain visual areas.

Utilizing the photically-evoked cortical potential as an index of neuronal activity in the visual system, we have attempted to assess the effects of both regional (raphe) and systemic LSD upon the visual evoked response and to clarify the role of serotonergic mechanisms in LSD-induced alterations in visual perception.

METHOD

Seventy adult male cats (2.5–4.0 kg) were anesthetized

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with an 80%–20% mixture of nitrous oxide-oxygen, supplemented with the volatile anesthetic fluoromar. The trachea was intubated and cannulae were inserted in the femoral vein and artery for drug administration and continuous monitoring of systemic blood pressure, respectively. The animal was mounted in a stereotaxic apparatus and all pressure points and skin margins were periodically infiltrated with lidocaine.

A 10 mm hole was trephined over the primary visual cortex (area 17) at coordinates of $A_{0.0}$,$L_{2.5}$ [23] to allow subsequent placement of a silver ball electrode. A stainless steel skull screw positioned over the frontal sinus served as the indifferent electrode. To implant a cannula in the dorsal raphe nucleus ($P_{0.5}$,$L_{0.0}$,$H_{-1.0}$) and to avoid penetrating the sagittal sinus, the device was inserted at an angle of 40° from the midsagittal plane and 20° caudally from the transverse vertical plane. The microinjection cannula assembly consisted of two parts: a thin walled 22 gauge outer guide cannula and a 28 gauge beveled inner injection cannula, which extended 1.0 mm below the guide.

The skeletal muscle relaxant decamethonium (1 mg/kg, IV) was administered immediately after termination of the anesthetic, and at 30-minute intervals thereafter, and the animal was artifically ventilated. In order to assure that the animal remained in a pain-free state, lidocaine was repeatedly applied to wound margins and the EEG was continually monitored using a Tektronix dual sweep oscilloscope (CRO), Type 564B and a Gross 7B polygraph. No significant hyperexcitatory pattern was detected in any animal during the experimental period. Further, blood pressure was recorded continuously with a Statham P_{23}AC pressure transducer and displayed on the Grass 7B polygraph, and remained stable in each animal during the recording period. End tidal CO_2, monitored by a CO_2 electrode with signals fed into a recording pH meter, was employed as an index of the blood gas spectrum and was maintained between 3.5 and 4.5 percent by adjusting the rate and volume of the respirator. Body temperature was monitored by a rectal thermistor and maintained between 37–39°C by means of a heating pad.

To afford maximal pupillary dilation and retraction of the nictitating membrane for optimal reception of the visual stimulus, atropine (0.5%) and phenylephrine (1.0%) were instilled in each eye approximately every 30 minutes. Physiologic saline was applied to each eye via a continuous drip assembly to minimize drying of the cornea and a local anesthetic was infiltrated periodically into the eye socket to further reduce unpleasant local sensations. Two to three hours elapsed between preparation of the animal and recording of brain electrical activity.

The Grass Model P_{15}B preamplifiers utilized in the study had a wide frequency band pass filter (1 to 300 Hz) to accommodate the frequency range of evoked potentials and a gain of approximately 1000. A Grass Stimulator (SD-5), which served as a pulse former, generating a DC square voltage wave of fixed duration directly triggered the CRO and drove the photostimulator (Grass PS_{22}) after a 200 msec delay. To initiate the visual evoked response, a stroboscopic flash of light (800,000 lumens;10 microseconds) was delivered to the eyes every five seconds throughout the course of the experiment. This intensity was determined to be supramaximal in our system based upon an experimentally determined stimulus-amplitude calibration curve and was selected so as to minimize the possibility of significant changes in evoked response amplitude resulting from slight fluctuations in stimulus strength.

Lysergic acid diethylamide, 5-hydroxytryptamine creatinine sulfate, and cinanserin hydrochloride were prepared in sterile distilled water (pH range 5.5–7.5), whereas *l*-tryptophan was initially triturated with Tween 80 and suspended in 4–5 ml physiologic saline. A micrometer driven syringe-injection apparatus was employed to deliver volumes of 2 to 4 μl (dependent upon solubility of the substances) into the raphe nucleus at a rate of 1 μl/minute. At the termination of each experiment, bromophenol blue (2 μl) was microinjected into all cannulated brain areas and the animal was sacrificed. The brain was rapidly removed, firmed in formaldehyde, and vertically sectioned and cannula placements were histologically verified by comparison to a reference atlas [23]. Of the 70 animals prepared, 36 were utilized for systemic injections and 30 for intraraphe injections; the remaining 4 animals evidenced inaccurate electrode placements upon histologic examination and were not used for data analysis. All animals received only one drug during the course of an experiment, except for those 16 animals who were given cinanserin 30 minutes prior to receiving either LSD (N=8) or 5-HT (N=8).

Pre-treatment responses were obtained at ten minute intervals for 30 minutes prior to drug injection by recording a series of ten consecutive evoked responses on Polaroid film. Peak to peak amplitudes of the three primary components of the evoked potential were measured for each of the ten responses and the values of all readings for each individual component were averaged. Following drug administration, amplitudes of the visually evoked response were continually monitored via the oscilloscopic tracing.

At frequent intervals (i.e., every 3–5 minutes) during the first 30–45 minutes after drug injection, i.e., the period during which amplitude changes attained maximal levels, ten consecutive evoked responses were recorded and measured as previously described. Data are reported as the maximal changes in the amplitudes of each of the three primary components compared to the respective averaged pre-treatment responses, expressed as a percent. Drug effects were evaluated for significance by comparing the maximal percent changes in the evoked response components following drug administration to the maximal percent changes in the same components following saline administration. Each mean percent change was compared to every other mean percent change in any one component using a separate two way analysis of variance.

RESULTS

Configurations of individual visually evoked responses (VER) recorded from the primary visual cortex consisted of an initial surface biphasic wave (small positive component and a larger negative segment) followed by two additional deflections (negative-positive, positive-negative) and a series of variable after discharges. The primary components were labeled as positive$_1$-negative$_1$, negative$_1$-positive$_2$, and positive$_2$-negative$_2$ (P_1-N_1, N_1-P_2, and P_2-N_2, respectively). The voltages of the first surface positive cortical potential were 150–400 μV with an onset latency of 7–15 msec.

To ascertain the variability inherent in potentials evoked throughout the period in which experimental observations were to be made, i.e., 240 minutes, a series of experiments were performed to derive the relationship between amplitude changes of the three primary components vs time in non-treated animals. No significant alterations were observed in any of the three components throughout the four hour observation period; maximal amplitude changes were −5.9%, +4.7%,

TABLE 1

EFFECTS OF INTRAVENOUS LYSERGIC ACID DIETHYLAMIDE (LSD) AND l-TRYPTOPHAN ON THE AMPLITUDE OF THE PRIMARY COMPONENTS OF THE PHOTICALLY EVOKED CORTICAL POTENTIAL

Treatment	Dose (IV)	N	Maximal Percent Change in Amplitude from Pre-treatment Level*		
			P_1N_1	N_1P_2	P_2N_2
Saline	1 ml	6	−0.9(4.6)	+4.7(2.2)	+3.1(2.7)
LSD§	0.7 μg/kg(0.1–1.0)	7	−2.2(9.9)	−5.8(8.6)	+6.3(11.1)
	4.7 μg/kg(1.0–10.0)	12	−6.7(10.2)	+8.7(6.7)	+22.6(12.9)
	28.8 μg/kg(10.0–100.0)	5	+24.0(5.3)‡	+25.9(7.6)†	+36.5(4.7)‡
l-Tryptophan	100 mg/kg	6	−19.1(4.3)‡	−23.2(6.8)‡	−19.4(5.6)‡

*Symbols (+) and (−) denote the maximal increase or decrease, respectively, in the amplitude of each component, averaged for the number of observations (±SE); p values represent significant differences from saline (†$p<0.05$; ‡$p<0.01$).

§Doses for LSD are given as the average for the indicated number of animals, with the range in parentheses.

+3.1% for the averaged (N=6) P_1-N_1, N_1-P_2 and P_2-N_2 components, respectively.

In order to assure that the "click" associated with each firing of the gas discharge lamp was not confounding the appearance of the photically evoked response, recordings were made while animals were shielded from all light emanating from the lamp and the responses compared to light-evoked potentials. No detectable evoked activity was evident in those animals shielded from the light source in response to the repetitive "clicking" of the discharge lamp. Although prolonged, high-intensity, repeated stimulation of the dilated eye might be expected to have some detrimental effects, the consistency of our evoked responses over the four hour observation period indicated that any pathological changes which may have occurred were probably minimal and did not alter the critical parameter being measured, i.e., evoked response amplitude.

Potentials in the primary visual areas of the cortex evoked by photic stimulation did not change significantly in amplitude after the IV administration of small doses of LSD (0.10–10 μg/kg; N=19) (Table 1). Larger doses of LSD (10–100 μg/kg; N=5) produced significant ($p<0.05$ compared to saline) increases in amplitudes of P_1-N_1, N_1-P_2, and P_2-N_2 components of +24.0%, +25.9%, and +36.5%, respectively within 15–20 minutes. In contrast, intravenous injection of l-tryptophan (100 mg/kg; N=6), a 5-HT precursor, decreased amplitudes of the three VER components 19.1%, 23.2%, and 19.4% from pretreatment levels ($p<0.01$). Peak effects occurred 30–40 minutes after l-tryptophan administration and persisted for up to 120 minutes. Although higher doses (200 and 400 mg/kg) of l-tryptophan elicited greater attenuation of the VER (maximal decreases of −31% and −43%, respectively), the potentials became unstable with increasing dosage, perhaps due to the blood flow alterations produced by these elevated doses. Saline (1 ml, IV; N=6) did not significantly alter the amplitudes of the evoked response components, average values for the maximal changes in each component being −0.9%, +4.7%, and +3.1%.

Intraraphe microinjections of LSD and 5-HT produced changes in evoked response amplitude similar in direction to those elicited following IV administration of LSD and l-tryptophan, respectively. LSD (0.25 μg; N=10) produced

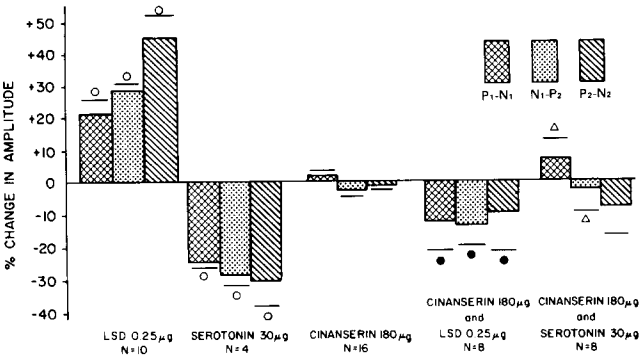

FIG. 1. Effects of intraraphe Lysergic Acid Diethylamide (LSD) and Serotonin on photically evoked cortical potentials and their modification by Cinanserin. Each bar represents the maximal amplitude change from the pre-treatment level of the averaged cortical response for each indicated component. Horizontal bars indicate standard errors. (○) denotes significant difference ($p<0.01$) from saline; (●) denotes significant difference ($p<0.01$) from LSD alone; (△) denotes significant difference ($p<0.05$) from serotonin alone.

maximal increases in the amplitudes of the first three components of the averaged cortical response of 21.2%, 28.6%, and 43.0%, respectively ($p<0.01$) within 10–20 minutes after injection (Fig. 1). Conversely, intraraphe 5-HT (30 μg; N=4) depressed all three components (−25.9%, −29.6%, −30.3%; $p<0.01$; Fig. 1), peak effects again occurring 10–20 minutes after injection. Saline (2 μl; N=17) did not elicit significant alterations in any of the evoked response components (−6.4%, −2.8%, −3.1%). Higher intraraphe doses of both LSD (0.5, 1, 10 μg) and 5-HT (60, 120 μg) failed to significantly increase the magnitude of the responses observed at the lower doses.

To determine serotonergic specificity of the above responses, cinanserin, a 5-HT antagonist, was microinjected into the raphe nucleus 30 minutes prior to LSD (0.25 μg, raphe), 5-HT (30 μg, raphe) or l-tryptophan (100 mg/kg, IV). Intraraphe cinanserin (180 μg; N=8) reversed LSD-induced

enhancements in all three components (+21.2%, +28.6%, +43.0% to −12.8%, −13.7%, and −9.6%, respectively; Fig. 1). Depressions of the VER observed after locally injected serotonin (30 μg) were also antagonized by cinanserin (180 μg; N=8), resulting in diminution and in one case (P_1-N_1) reversal of the response (−25.9%, −29.6%, −30.3% to +7.1%, −2.4%, −9.6%). Larger subsequent doses of LSD and 5-HT were able to partially overcome the effect of cinanaserin, indicating a competitive type blockade. Cinanserin-induced blockade of LSD was statistically significant for all three components ($p<0.01$), whereas significant antagonism of 5-HT was observed only in the first two components ($p<0.05$).

Conversely, intraraphe cinanserin (180 μg) failed to significantly antagonize the depressive effects of systemically administered *l*-tryptophan (100 mg/kg; N=6) on cortical evoked responses. The amplitude of the three components was not significantly altered by cinanserin alone (180 μg; N=16), average changes being +1.6%, −4.8%, −2.3%, respectively, during the 30 minutes preceding injection of LSD or 5-HT.

DISCUSSION

Following intravenous administration, LSD increased the amplitude of the three primary components of the VER, whereas *l*-tryptophan depressed the responses. The raphe complex has been postulated to play a role in regulating activity in the visual pathway, perhaps that of dampening the organism's response to external stimuli [13]. Anatomical evidence has revealed that several forebrain areas, including the lateral geniculate nucleus (LGN), a thalamic visual relay center, receive uniform raphe tryptaminergic projections [4, 9, 10]. Significantly, these forebrain areas receiving raphe innervation are largely inhibited by dorsal raphe activation [2,7]. Depression of a brain stem area (e.g., raphe) normally exerting an inhibitory influence on a forebrain area (e.g., LGN) would result in disinhibition of the forebrain structure; in this case, increased reactivity to optic stimuli manifested as augmented VER amplitude. Microelectrode recordings have shown that systemically administered [1,26] as well as iontophoretically applied [17] LSD reversibly inhibited neuronal firing within the dorsal raphe of both rats and cats. Inhibition was observed at rather low doses of LSD (10–50 μg/kg, IP) and was highly selective for raphe neurons. Similarly, the comparable IV doses of LSD (10–100 μg/kg) utilized in our study could have attenuated the tonic inhibitory action of the raphe on the visual pathway, resulting in the enhanced visual evoked activity that we observed.

The question of whether further increases are possible in an evoked response which is derived from "supramaximal" stimulus intensity must be considered. One must be careful in equating a supramaximal stimulus intensity with peak response amplitude. The stimulus intensity is of course independent of the animal and was selected, as indicated, so as to minimize response variation to slight changes in stimulus strength. The ER amplitude, conversely, is largely dependent on the state of the animal; thus, a peak response to a supramaximal stimulus in a control animal does not mean that further increases in ER amplitude to a constant stimulus will not occur if the tonic state of visual control centers is altered, such as following LSD administration. Thus, the fact that the response is at peak in a control animal does not preclude the possibility of further increases in amplitude as neuronal activity in visual modulatory centers is altered.

It is interesting to note that Trulson and Jacobs [26] observed a characteristic behavioral pattern in their cats at systemic doses of LSD comparable to those used in our investigation. Peak behavioral changes coincided temporally with peak changes in raphe neuronal activity, suggesting a causal relationship between LSD-induced modulation of raphe activity and the drug's ability to induce behavioral modification. Moreover, the latency for development of maximal behavioral effects, typically 15–20 minutes following a 50 μg/kg IP dose, closely paralleled the time required to produce maximal alterations in the VER in our animals following similar IV doses of LSD. Thus, behavioral modifications induced by systemic LSD may be related to actions on neuronal systems that also influence visual perception.

The depressant effects of systemic *l*-tryptophan on the VER might be due in part to increased activity in the raphe nuclei subsequent to enhanced regional 5-HT biosynthesis. Systemic *l*-tryptophan is selectively incorporated into raphe neurons and elicits an almost linear increase in central 5-HT biosynthesis at the dose employed [15,25]. Tryptophan-induced increases in raphe 5-HT levels could therefore intensify the inhibitory action of the raphe on visual forebrain areas. The slower onset of action of *l*-tryptophan compared to systemic LSD in altering the evoked response (30–40 minutes vs 15–20 minutes) might reflect the additional time needed to synthesize sufficient 5-HT in the raphe to enhance the dampening effect.

The influence of raphe activity on visually evoked cortical potentials was further assessed by microinjecting LSD and 5-HT directly into the dorsal raphe during photic stimulation. Intraraphe LSD augmented the VER whereas 5-HT diminished the response. Various investigators [3,24] have shown that microiontophoretically applied 5-HT predominately inhibited single unit firing in rostral raphe as well as reticular nuclei. Conversely, data from other experiments involving the reticular formation [8], and median and caudal raphe [12] of cats have revealed an excitatory action of 5-HT on single units within these areas although there is no direct evidence that these nuclei contain serotonergic neurons that project to visual forebrain areas. Our data, however, suggest that 5-HT, when applied directly to the raphe can activate the inhibitory forebrain projection neurons, thus attenuating the visual evoked potential. In contrast, microiontophoretically applied LSD reduces neuronal firing in the raphe nucleus [2,17] and blocks the excitatory response to iontophoretic 5-HT [7]. These reported depressant effects of LSD in the raphe closely align with our observations that intraraphe microinjections of LSD enhance the VER, presumably by impairing the serotonergic-mediated dampening action of the dorsal raphe on forebrain visual areas.

Cinanserin, an effective antagonist of 5-HT receptors in the CNS [5,19] was employed to evaluate the importance of selective 5-HT receptor interactions in the raphe for the observed drug-induced changes in cortical evoked potentials. Intraraphe cinanserin markedly attenuated the depressant effects of microinjected serotonin, completely reversed the enhancement of the VER following intraraphe LSD but only slightly diminished the depressant action of IV *l*-tryptophan. Cinanserin blockade was of a competitive nature, as larger subsequent doses of LSD and 5-HT were able to partially overcome the cinanserin antagonism, restoring the initial responses, although to a somewhat lesser amplitude. Thus, the modulatory effects of intraraphe LSD and 5-HT on the visual evoked response appear to be mediated by a direct tryptaminergic receptor interaction. The inability of cinanserin to significantly alter the depressant action of IV tryptophan

may reflect the inherent difficulty in blocking the action of an endogenously released neurotransmitter (i.e., 5-HT formed from tryptophan) or suggest the possibility that the effects of systemic *l*-tryptophan on the VER result from an action of the drug at multiple central sites.

The action of LSD was blocked to a greater degree than that of 5-HT, a finding which is in agreement with results obtained by Bennet and Snyder [6] who demonstrated cinanserin to be a more effective antagonist of LSD than of 5-HT binding in rat brain membranes and concluded that LSD and 5-HT receptors, although related, are probably not identical. Although our data do not provide direct evidence along these lines, the ability of cinanserin to completely reverse the effects of intraraphe LSD on the VER and at least partially reverse those of 5-HT suggest that more than one tryptaminergic receptor type may be present in the raphe nucleus.

Our findings indicate that modification of neuronal activity within the dorsal raphe nucleus can markedly alter photically evoked cortical responses. Enhancement of the VER following both systemic and intraraphe injection of LSD may result from disinhibition of visual forebrain raphe projection areas (e.g., LGN) subsequent to reduced neuronal activity in the dorsal raphe nucleus. Further, depression of raphe activity by LSD might offer an explanation for its hallucinogenic properties, namely perceptual disturbances resulting from depression of an area (i.e., raphe) normally inhibiting visual and possibly other sensory inputs.

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