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INHIBITORY EFFECTS OF STEROIDS ON LSD-25 ACTION IN MAN*

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Certain mental phenomena such as post partum psychoses and the transient remissions, occasionally reported in psychotic females during pregnancy, may be viewed as concomitants of changes in circulating steroid levels. Accordingly, we have investigated the effects of steroid hormones upon behavioral changes produced by a potent psychotomimetic agent, lysergic acid diethylamide (LSD-25). An earlier paper (1) summarized the results of the first of these studies, and presented evidence that the oral ingestion of 600 mg. progesterone one hour prior to administration of 75 mcg. LSD-25 significantly reduced the degree of behavioral change ordinarily induced by LSD-25 in certain objectively measured sensorimotor and perceptual behaviors. The present paper summarizes the results of studies investigating the efficacy of two synthetic steroids in altering the effects of LSD-25 on psychological behavior in humans. The steroids are 3,17 beta - diacetoxy - 17 alpha - prop - 1 ynyl - estra - 3,5 - dien (SC 10592) and 3 beta - propionoxy - 17 beta - hydroxy - 17 alpha - ethylestr - 4 - ene (SC 7294). These steroids are 19 nor-steroids with progestational activity; SC 10592 is a diacetate and SC 7294 is a monacetate.

As with the progesterone study, the expectation that these steroids should alter the effects of LSD-25 in humans is based on the findings of animal studies conducted by

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Bergen et al. (2), which demonstrated that the impairment in rope climbing ability in rats (Winter-Flataker Rope Climbing Test) ordinarily induced by LSD-25 is greatly decreased when LSD-25 administration is preceded by injection of the steroids employed in this study.

General Procedure

Two studies will be reported: one investigating 3,17 beta - diacetoxy - 17 alpha - prop - 1 - ynyl - estra - 3,5 - dien (SC 10592) and one investigating 3 beta - propionoxy - 17 beta - hydroxy - 17 alpha - ethylestr - 4 ene (SC 7294).

The behavioral tests employed in each study were drawn from a battery, described below, which was administered to each of 12 male subjects under each of four experimental conditions: placebo, steroid, LSD-25, and steroid preceding LSD-25. Since a double-blind technique was employed it was necessary that subjects be given what appeared to be identical agents on each testing day. This was accomplished by using the following regimen: (A) Placebo Day: Placebo tablets containing sodium bicarbonate followed one hour later by 75 mcg. LSD-25 in 20 ml. of water. (B) Steroid + LSD Day: 60 mg. steroid tablets followed one hour later by 75 mcg. LSD-25 in 20 ml. of water. (C) Steroid Day: 60 mg. steroid tablets followed one hour later by 20 ml. of water. (D) LSD-25 Day: Placebo tablets followed one hour later by 75 mcg. LSD-25 in 20 ml. of water.

For each of the studies on each day, then, subjects received a tablet (60 mg. of steroid or placebo) followed one hour later by approximately 20 ml. of colorless, odorless, tasteless liquid (placebo or LSD-25). Sequence and order effects of the experimental conditions were controlled by employing a 4 x 4 Latin square design replicated three times, i.e., three subjects in each of the four sequences, ABCD, DABC, CDAB, and BCDA. One week was interpolated between each of the experimental conditions. Testing began two hours after the oral ingestion of the 20 ml. of liquid.

Subjects. For each study, 12 normal, male, adult volunteers of average and above average intelligence were drawn from the personnel of the Worcester Foundation for Experi-

mental Biology. These subjects, some of whom participated in all three studies, ranged in occupation from maintenance worker to technical assistants to research scientists. Their ages ranged from 26 to 40 years with a mean of 31 years.

Experimental situations. The experimental situations utilized were chosen on two grounds; first, that the behavior tapped in the situation changes significantly under LSD-25; and second, that the degree of behavioral change be amenable to fairly precise objective measurement. Experimental situations satisfying these criteria were chosen from among those previously utilized in our ongoing research concerned with the behavioral effects of LSD-25 in normal and schizophrenic adults. It might be noted parenthetically, that these tests for the most part also differentiate between normals and schizophrenic (chronic) adults (see, e.g., Wapner and Krus (3); Krus et al. (4)); further, the nature of the differences between normals and schizophrenics parallels those found between normals (and schizophrenics) under placebo as compared to LSD-25 conditions. Twelve such situations -- sampling sensori-motor, perceptual and conceptual behavior -- were chosen for these studies.

1. Sensori-Motor Processes

(a) Two Hand Coordinator: in which subject must maintain contact between a movable button controlled by subject and a metal disc target traversing an irregular two-dimensional pattern independent of subject's control. Subject controls the movable button by two lathe handles, one of which actuates left-right movement, and one which actuates front-back movement through the medium of rack and gear devices. The score taken reflects the time subjects maintain coincidence between button and target during the 60 seconds comprising a trial. Under LSD-25, two-hand coordination as measured in this situation tends to decrease (5).

(b) Tapping Rate: in which subjects tap with a stylus at a speed comfortable to them. The score is the number of taps for a 15-second time interval. Under LSD-25,

tapping rate increases (6).

(c) Card Sorting: in which subjects deal a standard deck of 52 playing cards into two piles at a speed which seems natural to them. The score taken is the duration of time required for the task. Under LSD-25, card sorting speed decreases (6).

(d) Handwriting: in which subjects are required to write a standard phrase (United States of America) at their normal handwriting speed. Score taken is the time to write the phrase. Under LSD-25, handwriting speed decreases (6).

2. Perceptual Processes.

(a) Apparent Eye Level Test: in which subject must adjust to apparent eye level, while seated in a dark room, a black line horizontally bisecting a square patch of light. The score taken reflects the position of the apparent eye level in relation to objective eye level. Under LSD-25, apparent eye level is located higher than under placebo (7).

(b) Heiss-Sander Task: in which subjects must locate a designated part in a whole configuration made up of that part and other parts. The time taken by subject to extract the designated part from the whole is the score used. Under LSD-25, time taken to extract a part increases (8).

(c) Self Perception: in which subjects must estimate the size of their head at the temples by striking off on a meter stick presented horizontally in front of them the appropriate distance with their forefingers. Two trials are employed with the mean estimate of head size serving as the measure employed in the analysis. Under LSD-25 apparent head size increases (5).

3. Conceptual Processes.

(a) Simple Arithmetic: in which subjects must complete a series of simple addition problems (e.g., 1 + 2) at a speed which is comfortable to them. The score taken is the time subject requires for the task. Under LSD-25, speed of doing simple arithmetic

decreases (6).

(b) Complex Arithmetic: same as above except that the series of problems is more difficult (e.g., 23 + 18). The score taken is the time subject requires for the task. Under LSD-25, speed of doing complex arithmetic decreases (6).

(c) Stroop Color-Word Test; Card A: in which Ss are presented with a card containing 100 color-name words (red, green, blue) printed in black ink. S's task is to read the names of the colors as rapidly as possible. The score employed is the time taken to read the 100 color-name words on the card which increases under LSD-25 (3).

(d) Stroop Color-Word Test; Card B: in which Ss are presented with a card containing 100 color patches (red, green and blue) and are required to name the colors appearing on the card as rapidly as possible. Time taken to complete the task increases under LSD-25 (3).

(e) Stroop Color-Word Test; Card C: in which Ss are presented with a card containing 100 color-name words (red, green, blue) printed in an ink whose color is incongruent with the printed name. S's task is to name the color of ink in which the color-name words are printed (e.g., the word "blue" printed in green ink to which S must say "green" rather than "blue"). The score employed is the time taken by S to name the 100 ink colors on the card. Under LSD-25, time taken to complete this task increases (greater interference) (3).

Qualitative Observations. Subjects were asked after the study to compare (in retrospect) the two occasions on which they had had LSD-25. The experimenters also noted comments concerning subjective aspects of the experience on each test day.

Results

Quantitative data were examined in two ways. First, the mean scores obtained for each behavioral parameter under each of the four experimental conditions were viewed to see whether or not they fell in a predicted ordering. From previous work it was known

that mean scores for placebo and LSD-25 conditions should differ in directions specified earlier; the mean score for steroid + LSD-25 condition should fall between these two extremes if the expectation of steroid inhibition was supported. No prediction concerning the mean scores for steroid alone were made although on the basis of available evidence, there would be no compelling reason to expect these to differ significantly from placebo values. Tables 1 (SC 7294) and 2 (SC 10592) summarize the means for each experimental condition for each behavior assessed in the two studies, and indicate that mean values for placebo, steroid + LSD-25, and LSD-25 conditions fall in this predicted ordering for 9 of the 12 behavioral assessments in each study.

Quantitative data were also analyzed by means of Latin square analyses of variance to determine whether an overall influence of the experimental conditions was statistically evidenced. Wherever a significant overall effect for experimental conditions was found, "t" tests were employed to determine among which of the four condition means significant differences obtained. Tables 1 and 2, dealing with SC 7294 and SC 10592, respectively, summarize these analyses by indicating for each behavioral measure where a significant effect of experimental conditions was obtained, and indicate those behaviors for which the LSD-25 condition differs significantly from "placebo," as well as those behaviors for which the "steroid + LSD-25" condition differs significantly from "LSD-25" in the expected direction toward "placebo." Results of these examinations of the data may be summarized as follows:

1. SC 7294 (Table 1)

(a) As mentioned, means for placebo, steroid + LSD-25, and LSD-25 conditions were in the predicted order in 9 of the 12 situations.

(b) Significant LSD-25 effects were found (replication of previous work) in 7 of the 12 experimental situations.

(c) SC 7294, orally administered, counteracted LSD-25 effects in 4 of the 7

TABLE 1

Counteractive Effects of Steroids on LSD-25

SC 7294 Orally Administered

Experimental Situation	Test Conditions (Means)				t-tests	
	Placebo	SC 7294	SC 7294 + LSD-25	LSD-25	LSD-25 vs. Placebo	LSD-25 vs. SC 7294 + LSD-25
1. Two Hand Coordination: Time (secs.)	48.5	47.6	45.6	41.8	sig.	sig.
2. Tapping Rate: Taps/15 secs.	62.1	64.0	60.1	67.9	--	--
3. Card Sorting: Time (secs.)	25.0	25.2	27.1	27.9	--	--
4. Handwriting: Time (secs.)	48.4	46.8	40.4	49.5	--	--
5. Apparent Eye Level = cms. above (+) or below (-) objective eye line	+4.7	+5.4	+9.4	+9.7	--	--
6. Heiss-Sander: Time (secs.) to locate part	3.4	3.3	4.2	4.4	sig.	--
7. Apparent Head Size (cms.)	22.2	23.0	25.1	26.6	--	--
8. Simple Arithmetic: Time (secs.) to do problems	53.5	54.1	63.5	62.3	sig.	--
9. Complex Arithmetic: Time (secs.) to do problems	79.4	80.7	92.8	98.0	sig.	--
10. Stroop Card A: Time (secs.)	43.8	43.5	48.1	52.1	sig.	sig.
11. Stroop Card B: Time (secs.)	58.5	59.8	67.2	77.7	sig.	sig.
12. Stroop Card C: Time (secs.)	98.8	99.2	111.7	126.3	sig.	sig.

TABLE 2

Counteractive Effects of Steroids on LSD-25

SC 10592 Orally Administered

Experimental Situation	Test Conditions (Means)				t-tests	
	Placebo	SC 10592	SC 10592 + LSD-25	LSD-25	LSD-25 vs. Placebo	LSD-25 vs. SC 10592 + LSD-25
1. Two Hand Coordination: Time (secs.)	49.0	48.5	46.4	48.6	--	--
2. Tapping Rate: Taps/15 secs.	85.4	85.1	86.2	77.6	--	--
3. Card Sorting: Time (secs.)	22.9	22.9	23.8	25.3	--	--
4. Handwriting: Time (secs.)	45.8	44.8	48.8	52.6	sig.	--
5. Apparent Eye Level = cms. above (+) or below (-) objective eye line	-7.7	-9.7	-5.1	-6.3	--	--
6. Heiss-Sander: Time (secs.) to locate part	4.6	4.3	5.2	5.5	--	--
7. Apparent Head Size (cms.)	15.6	15.8	17.8	18.4	--	--
8. Simple Arithmetic: Time (secs.) to do problems	49.6	52.2	57.2	65.2	sig.	--
9. Complex Arithmetic: Time (secs.) to do problems	71.3	74.4	88.1	96.1	sig.	--
10. Stroop Card A: Time (secs.)	42.6	41.7	49.1	51.3	sig.	--
11. Stroop Card B: Time (secs.)	57.7	56.8	67.7	73.5	sig.	sig.
12. Stroop Card C: Time (secs.)	50.6	47.5	55.8	63.2	sig.	sig.

situations in which significant LSD-25 effects were found. These include: two hand coordination, word reading (Stroop A), color naming (Stroop B), and resisting interference (Stroop C).

2. SC 10592 (Table 2)

(a) Means for placebo, steroid + LSD-25, and LSD-25 conditions were in the predicted ordering in 9 of the 12 situations.

(b) Significant LSD-25 effects were found (replicated) in 6 of the 12 experimental situations.

(c) SC 10592, orally administered, counteracted LSD-25 effects in 2 of the 6 situations in which significant LSD-25 effects were found. These are: color naming (Stroop B) and resisting interference (Stroop C).

Qualitative Observations. Although some evidence is found that objectively measured behavioral effects of LSD-25 were attenuated as described in the preceding, it is noteworthy that the majority of subjects could not subjectively distinguish the LSD-25 day from the LSD-25 plus steroid day. The commonly reported experience was that "I felt just as high on both days." The experimenters could not detect differences between these conditions either, when observing such gross behavioral manifestations of effects as mood changes, pacing, giggling, etc. All subjects and the experimenters, however, could easily distinguish days involving LSD-25 from the placebo and steroid days.

Comment. There is some evidence in these studies, analogous to those of the animal studies and the study of the inhibiting effect of progesterone on LSD-25 in humans mentioned earlier, to suggest that the magnitudes of some behavioral changes found to occur following ingestion of LSD-25 are reduced when such ingestion is preceded by administration of certain steroids. Both SC 7294 and SC 10592, when orally administered, operated to inhibit the effects ordinarily induced by LSD-25 in certain situations. In the case of 7294, four behaviors (two hand coordination, word reading, color naming, resist-

ing interference) were identified in which ingestion of the steroid decreased the behavioral change ordinarily induced by LSD. With respect to SC 10592, analogous effects were demonstrated in two behaviors (color naming and resisting interference). This latter steroid, on the basis of the studies reported, does not appear to be as efficacious an inhibitor as either progesterone or SC 7294.

Contrasting the results of this study with the results of two other studies recently conducted in our laboratories leads to a further point worthy of discussion. Resnick et al. (9, 10) studied the effects of pretreatment with isocarboxazide and reserpine on LSD-25 effects in normal subjects. Results of these studies are, in one sense, strikingly different insofar as the attenuation and potentiation of the LSD-25 experience found under isocarboxazide and reserpine, respectively, were dramatically manifest in both objectively measured behavioral effects as well as in subjective experience. In contrast, the antagonistic effects of steroid pretreatment are only manifest when objective behavioral assessments are examined. Conceivably, this difference may lie in the fact that with the steroid only a single administration was given, whereas in the isocarboxazide and reserpine experiments, chronic administrations were given. It is well known that the steroids do not pass the blood-brain barrier rapidly; it is conceivable, then, that a single dose would not achieve the maximal effects that chronic pretreatment might.

Summary

Studies investigating the efficacy of two steroids in altering the effects of LSD-25 on psychological behavior in humans are presented. Results obtained by the experimental assessment of behavioral change in basic sensori-motor, perceptual and conceptual processes indicate some evidence of an inhibitory effect of the steroids on the degree of behavioral change ordinarily induced by LSD-25 in certain behaviors; however, results obtained from subjective reports fail to indicate inhibition of the LSD-25 effect. These results are shown as similar to results obtained in a previous study of the influence of progesterone in

altering LSD-25 effects in man, and in contrast to results of recently reported studies in which the attenuation or potentiation of the LSD-25 experience by pretreatment with a monoamine oxidase inhibitor or amine releaser, respectively, was manifested both subjectively and as objectively measured in the same experimental situations as utilized in the steroid studies. The possible role of acute as compared to chronic administration is discussed in relation to this disparity in results.

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