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The Influence of Progesterone on Behavioral Changes Induced by Lysergic Acid Diethylamide (LSD-25) in Normal Males*

By

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This paper summarizes the results of the first of a series of studies on the influence of certain steroids in altering the effects of LSD-25[1] on psychological behavior in humans. The expectation that these steroids should alter the efficacy of LSD-25 in inducing behavioral changes in humans was derived from a number of animal studies (BERGEN et al. 1959; BERGEN and PINCUS 1960; BERGEN et al. 1960) which demonstrated first, that learned rope climbing in rats is temporarily impaired by LSD-25; and, second, that injection of certain steroids prior to LSD-25 administration inhibits the decrement in rope climbing ordinarily induced by LSD-25 alone. Of the variety of steroids studied, progesterone appeared to be one of the most potent in antagonizing this effect of LSD-25. Accordingly, it was chosen as the first steroid to be explored in our program concerning the efficacy of various agents in counteracting behavioral changes in humans demonstrated to be induced by LSD-25.

The general expectation in this study, then, was that progesterone would reduce the degree of behavioral change normally induced by LSD-25. While the counteractive effect of progesterone on LSD-25 was the primary focus of this investigation, the experimental design was such as to allow assessment of the possible psychological effects of progesterone alone as well as replicate some of our previous findings concerning the behavioral effects of LSD-25 (WAPNER and KRUS 1960b).

Method

Subjects. Twelve normal male adult volunteers of average and above average intelligence drawn from the personnel of Worcester Foundation for Experimental Biology participated in the study. Four Subjects were maintenance workers, four technical assistants and four research scien-

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[1] LSD for this study, supplied by Sandoz Pharmaceuticals, Hannover, N J., was d-lysergic acid diethylamide tartrate in sealed ampules containing 0.1 mg. per ml.

tists. Their ages ranged from 26 to 38 years with a mean of 31 years. Subjects were screened to insure that none had a past history of emotional upset.

Experimental situations. The experimental situations utilized in this study were chosen on two grounds; first, that the behavior tapped in the situation change significantly under LSD-25; and second, that the degree of behavioral change be amenable to precise objective measurement. Experimental situations satisfying these criteria were chosen from among those previously utilized in the ongoing program of research at the Clark University laboratories concerned with the behavioral effects of LSD in normal and schizophrenic adults. Eleven situations — sampling sensori-motor, perceptual and conceptual behavior — were chosen to comprise the test battery employed in this study.

Sensori-motor Processes. 1. Steadiness Test: in which subjects must hold a stylus in a series of holes graded from large to small without touching the sides of the hole. The score taken is the number of times subjects touch the side of the hole for a 15-second trial in each of 5 holes. Under LSD it has been found that steadiness decreases (WAPNER and KRUS 1960b).

2. 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, two hand coordination as measured in this situation tends to decrease (WAPNER and KRUS 1960b).

3. 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, tapping rate increases (WAPNER and KRUS 1960b).

4. 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, card sorting speed decreases (WAPNER and KRUS 1960b).

5. 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, handwriting speed decreases (WAPNER and KRUS 1960b).

Perceptual Processes. 1. Apparent Horizon: in which subjects must adjust to apparent eye level in a dark room a black line horizontally bisecting a square patch of light. The score taken reflects the position

of the apparent horizon (apparent eye level) in relation to objective eye level. Under LSD, the influence of the position of the black line at the start of a trial is greater (final adjustment is closer to initial setting (WAPNER and KRUS 1960b).

2. 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, time taken to extract a part increases (KRUS and WAPNER 1959).

Conceptual Processes. 1. 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, speed of doing simple arithmetic decreases (WAPNER and KRUS 1960b).

2. 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, speed of doing complex arithmetic decreases (WAPNER and KRUS 1960b).

3. Stroop Color-Word Test: in which subjects 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. Subject'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 subject must say "green" rather than "blue"). The score employed is the time taken by subject to name the 100 ink colors on the card. Under LSD, time taken to complete this task increases (greater interference) (WAPNER and KRUS 1960a).

4. Raven Progressive Matrices Test: in which subjects must abstract a general principle involved in a series of geometric designs in order to pick from a group of alternative designs the correct one to complete the series. The score taken reflects the time required to complete the test. Under LSD, time taken to complete the test increases (WAPNER and KRUS 1960b).

Procedure. The above battery of tests was administered to each of 12male subjects under each of four experimental conditions: placebo, progesterone, LSD, and progesterone preceding LSD. 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 orally administered:

(A) Placebo Day: Placebo tablets containing 600 mg. sodium bicarbonate (four 150 mg. tablets) followed one hour later by 20 ml. of water.

(B) Progesterone + LSD Day: 600 mg. progesterone (four 150 mg. tablets) followed one hour later by 75 γ LSD in 20 ml. of water.

(C) Progesterone Day: 600 mg. progesterone (four 150 mg. tablets) followed one hour later by 20 ml. water.

(D) LSD Day: 600 mg. sodium bicarbonate tablets (four 150 mg. tablets) followed one hour later by 75 γ LSD in 20 ml. of water.

On each day, then subjects received 600 mg. (four 150 mg. tablets) of identically appearing pills followed one hour later by approximately 20 ml. of colorless, odorless, tasteless liquid. Sequence and order effects

Table 1. *Analyses of Variance*
Experimental situations

Source of variation	df	1. Steadiness		2.Two Hand Coord.		3. Tapping Rate		4. Card Sorting	
		Mean Square	F	Mean Square	F	Mean Square	F	Mean Square	F
Bet. Ind's (l)	11	6846.9	<1.0	122.8	2.06	1559.5	1.24	49.5	<1.0
Sequence	3	1611.7	<1.0	291.6	4.90[1]	2390.5	1.92	31.4	<1.0
l/Seq. . .	8	8810.2	—	59.5	—	1247.9	—	56.2	—
Order . . .	3	1297.7	<1.0	145.2	9.61[1]	16.4	<1.0	2.6	<1.0
Conditions .	3	5114.1	4.0[1]	48.4	3.22[1]	210.4	1.07	19.1	6.86[1]
Sq. Uniq. .	6	617.9	<1.0	2.4	<1.0	56.6	<1.0	2.4	<1.0
Residual . .	24	1276.8	—	15.1		196.4	—	2.8	—
Total . . .	47	2742.6	—	49.2		487.1	—	14.7	—

Source of variation	df	5. Handwriting		6. Horizon		7. Heiss-Sander		8. Simple Arith.	
		Mean Square	F	Mean Square	F	Mean Square	F	Mean Square	F
Bet. Ind's (l)	11	595.4	1.01	94.1	<1.0	17.8	1.08	585.1	1.07
Sequence	3	611.7	1.04	75.7	<1.0	21.7	1.33	690.9	1.27
l/Seq. . .	8	589.2	—	101.0	—	16.4	—	545.4	—
Order . . .	3	12.6	<1.0	108.3	4.73[1]	41.0	7.17[1]	215.9	7.55[1]
Conditions .	3	17.8	1.34	166.5	7.28[1]	10.2	1.79	168.7	5.90[1]
Sq. Uniq. .	6	5.6	<1.0	70.6	3.09[1]	6.1	1.05	13.2	<1.00
Residual . .	24	13.3	—	22.9	—	5.7	—	28.6	—
Total . .	47	148.8	—	60.3	—	11.1	—	177.8	—

Source of Variation	df	9. Complex Arith.		10. Stroop		11. Raven	
		Mean Square	F	Mean Square	F	Mean Square	F
Bet. Ind's (l)	11	3912.6	<1.0	893.8	1.02	239108.6	1.05
Sequence	3	1975.9	<1.0	947.6	1.08	272060.9	1.19
l/Seq. . .	8	4638.8	—	873.6	—	226751.5	—
Order . . .	3	546.4	8.87[1]	1431.8	18.64[1]	489932.1	6.12[1]
Conditions .	3	447.7	7.27[1]	564.1	7.34[1]	90182.9	1.13
Sq. Uniq. .	6	87.4	1.41	144.2	1.88	71705.0	<1.0
Residual . .	24	61.6	—	76.8	—	80087.8	—
Total . . .	47	1021.8	—	394.2	—	143039.9	—

[1] $P < 0.05$.

of the experimental conditions were controlled by employing a 4×4 latin square design replicated 3 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 was begun two hours after the oral ingestion of the 20 ml. of liquid.

Results

Data were treated by computing a separate analysis of variance for each of the eleven experimental situations (Table 1). Results of these analyses are presented in summary form in Tables 2 and 3. Table 2 presents the mean scores and standard deviations for each of the dependent variables under each of the experimental conditions. Table 3 presents a summary of the analyses of variance performed on the data from each of the experiments, as well as an indication of whether the "progesterone" and "progesterone + LSD" conditions differed signifi-

Table 2. *Summary of Mean Scores and Standard Deviations*

Experimental Situation		Test Conditions			
		Placebo	Progesterone	Progesterone + LSD	LSD
1. Steadiness: No. of Hits (High Score indicates Unsteadiness)	M	22.2	32.2	38.1	70.0
	S.D.	25.5	47.8	44.4	67.5
2. Two Hand Coordinator: Time on Button Correctly (High Score indicates Greater Coordination)	M	49.8	47.8	46.5	45.1
	S.D.	4.4	6.9	8.8	5.9
3. Tapping Rate: Taps/15 secs (High Score indicates Faster Tempo)	M	71.2	69.3	76.8	78.4
	S.D.	19.0	23.3	24.3	19.0
4. Card Sorting: Time (secs) (High Score indicates Slow Speed)	M	23.7	24.9	24.2	26.6
	S.D.	3.6	3.6	3.3	3.9
5. Handwriting: Time (secs) (High Score indicates Slow Speed)	M	51.9	50.6	49.9	50.9
	S.D.	11.4	11.2	12.0	13.3
6. Horizon: Starting Position Effect in cms (High Score indicates Greater Effect)	M	9.5	12.5	11.8	18.2
	S.D.	7.3	5.4	7.7	7.4
7. Heiss-Sander Task: Time to locate part (secs) (High Score indicates Slow Speed)	M	8.1	8.0	9.8	9.6
	S.D.	2.2	2.1	5.2	2.3
8. Simple Arithmetic: Time (secs) to do problems (High Score indicates Slow Speed)	M	55.4	55.8	60.9	62.9
	S.D.	11.3	13.8	14.0	11.8
9. Complex Arithmetic: Time (secs) to do problems (High Score indicates Slow Speed)	M	81.2	81.0	89.1	92.6
	S.D.	30.6	33.8	29.9	30.2
10. Stroop Test: Time (secs) to read interference Card (High Score indicates high interference)	M	89.1	92.4	100.8	105.1
	S.D.	13.8	17.8	22.3	19.9
11. Raven Test: Time to do test (secs) (High Score indicates Slow Speed)	M	449	540	573	659
	S.D.	102	291	345	569

Table 3. *Summary of Analyses of Variance*

Experimental Situation	Means in expected direction?	F ratio reflecting between conditions variance significant?	"t" test between "LSD" and "Progesterone + LSD" significant?
1. Steadiness	yes	yes	yes
2. Two Hand Coordinator	yes	yes	no
3. Tapping Rate	yes	no	no
4. Card Sorting	yes	yes	yes
5. Handwriting	no	no	no
6. Apparent Horizon .	yes	yes	yes
7. Heiss-Sander Task . .	no	no	no
8. Simple Arithmetic . .	yes	yes	no
9. Complex Arithmetic .	yes	yes	no
10. Stroop Test	yes	yes	no
11. Raven Test	yes	no	no

cantly from each other. This latter result is based upon a *t*-test of the significance of the differences between the means for each of these conditions based on the residual from the analysis of variance of the particular experimental situation.

The findings may be summarized as follows:

1. As can be seen from an examination of the means in Table 2 and the number of significant F ratios listed in Table 3, our previous findings concerning the direction of effect of LSD versus placebo was replicated in 10 of the 11 experiments, though "*t*" tests of the difference between placebo and LSD means were significant in only 7 of these.

2. With respect to the main problem of this study, i.e., whether progesterone would reduce the degree of behavioral change attributed to LSD, two findings are of pertinence: First, examination of Tables 2 and 3 indicates that in 9 of the 11 experiments the mean scores fall in the predicted direction, i.e., the mean score for the progesterone-LSD condition falls between the mean scores for the placebo and LSD conditions. Second, as can be seen from the summary of *t*-tests in the right hand column of Table 3, the differences between the mean scores for the LSD condition as compared to the progesterone + LSD condition are significant below the .05 level of confidence for 3 of these 9 situations.

3. While the question of whether progesterone itself has a behavioral effect is not the main concern of this study, comparison of behavior under progesterone and placebo is pertinent to this problem. Though none of the differences between the mean scores for the progesterone and placebo conditions are significant, it is interesting to note that there is a consistency to the direction of the differences. In 8 of the 11 experimental situations (all but situations 3, 7, and 9). the direction of dif-

ference between progesterone and placebo is the same as that between LSD and placebo. This trend is supported by some qualitative observations. Some subjects, for example, reported feelings of irritability, slowness and general depression on the days they had received progesterone. All of this suggests that it might be worthwhile to investigate more intensively whether progesterone alone induces behavioral changes.

Discussion

There is some evidence from this study, analogous to those of the animal studies mentioned earlier, to suggest that the magnitudes of behavioral changes found to occur following ingestion of LSD are reduced when LSD ingestion is preceded by ingestion of progesterone. Moreover, for the most part, this applies to behavior representing the sensorimotor and perceptual as well as conceptual levels of organization. Thus, the antagonistic effects of progesterone on LSD are not restricted to lower animals, or to a single area of behavioral functioning.

It should be noted that the nature of the relationship between progesterone and LSD is not delineated by these studies but will depend upon further research. Such research will have to consider, for example, whether progesterone merely slows in time the onset of maximal LSD effect, or whether it reduces the absolute magnitude of such effects. Since our studies employed a fixed sequence of experimental situations administered after approximately the same interval post drug ingestion, we have no evidence concerning this problem. Such evidence could be gathered in studies which would enable us to plot onset and recovery curves of the changes in behavior induced separately by progesterone and by LSD, as well as in interaction with each other.

Somewhat related to this problem is the question of whether or not progesterone in and of itself has an effect upon behavior. While progesterone is usually assumed to be inert insofar as psychological changes are concerned, there is a suggestion in the present study from the results presented above that this assumption might be questionable.

Answers to some of the preceding questions should enable us to more adequately conceptualize the psychological effects of progesterone as well as the nature of the interaction between progesterone and LSD. In previous publications, LSD has been viewed as a pharmacological means of inducing behavioral regression (Wapner and Krus 1960b), i.e., as a primitivizing agent which would be expected to lead to less mature behavior. From this viewpoint, the nature of the interaction between progesterone and LSD could be posed in terms of the question of whether or not there are agents like progesterone which arrest or perhaps reverse developmental regressions.

Summary

The influence of a steroid, progesterone, in altering the effects of LSD-25 on psychological behavior in normal male humans was investigated in this study. Some evidence was found that the magnitude of changes found to occur under LSD-25 in behavior representing sensori-motor, perceptual and conceptual levels of organization, was reduced when LSD ingestion was preceded by progesterone ingestion.

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