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Action of Steroids on Lysergic Acid Diethylamide (LSD) Metabolism.* (27813)

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We have previously reported that natural steroids affect LSD action in trained rats(1), human volunteer subjects(2) and in a brain function, the optically evoked primary cortical potential of rabbits(3). In addition, prednisone, a synthetic steroid, is an effective antagonist of some phases of the LSD reaction in humans, according to Abramson and Sklarofsky(4). In order to learn more about LSD-steroid interaction, we have studied the metabolism of LSD *in vitro*.

Methods. Male Holtzman rats weighing 200-250 g were sacrificed by decapitation and 2-3 g of liver removed. To each liver sample 4 volumes of chilled isotonic KCl solution were added and the liver homogenized in a Potter-Elvehjem apparatus. A supernatant fraction containing microsomes and soluble fraction was prepared by centrifugation at 10,000 *g* for 15 minutes(5). Fractions from 200 mg of liver were incubated in a Dubnoff metabolic incubator at 37°C for 2 hours in a medium containing 35 μmol fumarate, 16 μmol glucose-6-phosphate, 1 unit glucose-6-phosphate dehydrogenase, 3.7 μmol TPN, 20 μmol $MgCl_2$, 0.32 μmol LSD and 660 μmol phosphate buffer pH 7.9 to make a final volume of 3 ml. Free steroids were suspended in a suitable vehicle† and added to the flasks to make final concentrations of 1×10^{-3} M and 1×10^{-7} M. Estimations of LSD remaining in the flasks after incubation were made according to the method of Axelrod *et al.*(5).

Results. Additions of LSD to the liver fraction and medium followed immediately by extraction and estimation of the recovered LSD resulted in 100% recovery of the LSD. Possible effects of the steroid suspending vehicle were assessed by comparison of LSD utilization in complete systems with and without addition of vehicle. No differences in LSD utilization between the two were noted.

Inhibition of LSD metabolism by a representative steroid, progesterone, at increasing dilutions is shown in Fig. 1. After demonstrating the inhibitory property of progesterone in detail, other steroids were tested at 2 dose levels. These results are shown in Table I. The degree of inhibition was found to be greatest for the adrenal cortical hormones and least for Dehydroepiandrosterone.

In addition to the use of liver homogenates, several experiments were performed using liver slices and brain slices. Liver slices me-

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† Suspending vehicle Special Formula No. 17874 (SV No. 17874) which consists of an aqueous solution of sodium chloride (0.9%) polysorbate 80 (0.4%), carboxymethylcellulose (0.5%) and benzyl alcohol (0.9%).

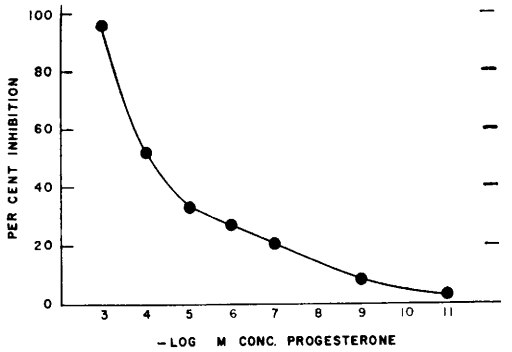

FIG. 1. Progesterone inhibition of LSD metabolism by a rat liver homogenate. Incubation conditions described in text.

tabolized LSD almost as well as homogenates but no utilization could be detected using brain slices. Axelrod *et al.*(5) likewise found that guinea pig brain slices did not metabolize LSD.

Discussion. The effectiveness of a variety of steroid substances to inhibit LSD metabolism at concentrations of 10^{-7} M indicates that steroids are powerful inhibitors of the enzymatic conversion of LSD to its metabolites.

Axelrod *et al.*(5) reported inhibition of LSD metabolism *in vitro* by serotonin and tranquilizing agents (reserpine, chlorpromazine and SKF 525) which were previously shown to have biologic interactions with LSD (6,7). In experiments with rats trained to climb a rope for a food reward, we have found that LSD administration greatly impairs the rope climbing ability. In contrast, rats pretreated with certain steroids for 3 days prior to LSD administration show no alteration in climbing ability due to steroid administration and significantly less impairment of function when challenged with LSD (1). Psychological investigations with volunteer human subjects show that psychomotor, conceptual and perceptual processes are altered by LSD administration but that these alterations are less in subjects pretreated with steroid substances(2). Our studies on the optically evoked primary response in rabbits show that LSD and the steroid, progesterone, act in a similar fashion to stabilize the response but that in combination the effects of the two drugs are not additive.

TABLE I. Per Cent Inhibition of LSD Metabolism by Steroids.

Compound	Molar concentration 1×10^{-3}	1×10^{-7}
Progesterone	96	20
Pregnenolone	100	65
Pregnandiol	76	63
Desoxycorticosterone	85	62
Dehydrocorticosterone	100	43
Corticosterone	84	73
Cortisol	76	67
Cortisone	100	88
11-Desoxycortisol	89	58
Testosterone	71	29
Androsterone	100	51
Δ^4 Androstenedione	100	66
Dehydroepiandrosterone	67	27
Estradiol	92	56
Etiocholanolone	97	24

An explanation for the effect of steroids compatible with the data from the rat behavioral tests, human psychological tests, rabbit electrophysiological tests and rat liver *in vitro* experiments is that LSD and steroids compete for the same cellular site of action and that steroids suppress the action of LSD at the enzymatic level.

Summary. A method is described which permits the biotransformation of LSD by a rat liver homogenate fraction. The rate of biotransformation is reduced significantly by steroids at concentrations as low as 10^{-7} M. The view is expressed that steroids block the action and metabolism of LSD by interfering with the LSD-receptor relationship in the cell.

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