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PROTECTION AGAINST LSD BY VARIOUS STEROIDS

H. Selye

Institut de médecine et de chirurgie expérimentales
Université de Montréal, Montreal, Canada

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SUMMARY

In rats, the dyskinesia elicited by a severe LSD intoxication was well prevented by pregnenolone-16α-carbonitrile (PCN), CS-1, ethylestrenol, norbolethone, prednisolone, triamcinolone and estradiol, but only just significantly by progesterone and phenobarbital. It is evident that steroids greatly differing in their classic hormonal, as well as in their enzyme-inducing, capacities can offer considerable protection against LSD intoxication.

Several excellent reviews (1, 2) deal with the pharmacology and toxicology of lysergic acid diethylamide (LSD). From these, it is evident that many of the effects of LSD may be counteracted in man and animals by chlorpromazine and other phenothiazines. Reserpine, on the other hand, appears to exacerbate the symptoms of LSD intoxication. Distribution studies with ^{14}C-labelled LSD showed that it is concentrated in the liver, but relatively little is found in the brain. It appears to be excreted by the liver in the form of 2-oxy LSD (3).

Comparatively little is known about the effect of steroids upon LSD intoxication. In rabbits, the EEG changes produced by LSD are said to be prevented by hydroxydione, androstanolone and, to a lesser extent, by 19-nortestosterone and methylandrostanolone (4, 5, 6). Both LSD and progesterone alter the characteristics of optically evoked cortical potentials in this species. Progesterone also inhibits LSD metabolism in an in vitro system; hence "it may be postulated that both drugs act on common cellular sites. It is suggested that progesterone may block the action of LSD by interfering with the LSD-receptor relationship of the cell" (7).

In rats, the behavioral changes induced by LSD could be suppressed by desoxycorticosterone (DOC), corticosterone, 17-dehydrocortisone, 11-dehydrocortisol, dehydroisoandrosterone, testosterone, androsterone, pregnenolone, etiocholanolone and progesterone. Other naturally occurring steroids tested were ineffective (8). The time required by a rat to climb a rope for a food reward is prolonged by LSD. This behavioral change is counteracted by pretreatment during three days with i.p. injections of dehydroisoandrosterone, androstenedione, cortisol, progesterone, testosterone, pregnenolone, DOC, dehydrocorticosterone, androsterone, etiocholanolone, corticosterone and 11-desoxycortisol, approximately in decreasing order of activity. Of all steroids tested, only estradiol was inactive in this respect (8, 9).

During the past few decades, countless observations have shown that steroids play a decisive role in determining the resistance of the body against the most varied types of injury. In this respect, they can be classified according to their mechanism of action into two main groups: (a) "syntoxic" steroids which improve tissue tolerance by permitting a symbiotic type of coexistence with the pathogen (e.g., by suppressing nonspecific inflammatory or allergic reactions against it), and (b) "catatoxic" steroids which actually destroy the aggressor (e.g., through the induction of hepatic microsomal or other enzymes). The syntoxic effects are virtually limited to glucocorticoids, whereas the catatoxic properties appear to be quite independent of any other known steroid hormone action (10). Thus, pretreatment with such catatoxic steroids as spironolactone, ethylestrenol, norbolethone and many steroid carbonitriles has been shown to offer protection against the subsequent administration of digitoxin (11), mercury (12), pesticides (13), carcinogens (14), nicotine (15), excessive amounts of steroid hormones (16,17), tyrosine (18), and well over 100 other toxicants widely differing in their chemical structure and pharmacologic actions (10). These findings suggest interesting clinical applications in the prevention of diseases caused by exogenous or endogenous intoxications.

Based on these observations, we undertook to examine the influence of various steroids upon LSD intoxication in comparison with several control substances, such as thyroxine (known to affect numerous forms of microsomal enzyme induction) and phenobarbital (one of the most potent nonsteroidal en-

zyme inducers of this type).

Materials and Methods

Female ARS/Sprague-Dawley rats (Madison, Wisc., U. S. A.) with an initial body weight of 100 g (range 90-110g) were maintained exclusively on Purina Laboratory Chow and tap water, divided into 15 groups and treated as outlined in Table I. To obtain the best catatoxic effect, it is important to allow a few days of pretreatment; hence, all animals received D-lysergic acid diethylamide (LSD) at the dose of 100 μg per 100 g body weight, in 1 ml water i.v., once, on the 4th day of treatment with the potentially protective substances.

The following steroids were tested for possible protective or sensitizing effects :

PCN [3β-Hydroxy-20-oxo-5-pregnene-16α-carbonitrile (Searle)],
CS-1* [9α-Fluoro-11β,17-dihydroxy-3-oxo-4-androstene-17α propionic acid potassium salt (Searle)],
Ethylestrenol (Organon),
Spironolactone (Searle),
Norbolethone (Wyeth),
Oxandrolone (Searle),
Prednisolone acetate (Roussel),
Triamcinolone (Lederle),
Progesterone (Schering),
Estradiol (Roussel),
Desoxycorticosterone acetate (Schering),
Hydroxydione sodium hemisuccinate (Pfizer).

All steroids were administered at the dose level of 10 mg in 1 ml water (homogenized with a trace of Tween 80), p.o., twice daily, throughout the period of observation.

L-thyroxine (B.D.H.) was injected subcutaneously (in the form of its sodium salt) at the dose of 200 μg in 0.2 ml water, once daily, and phenobarbi-

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* For Catatoxic Steroid Number 1. (Manufacturer's code number: SC-11927) The first nonhormonal steroid shown to possess catatoxic activity.

tal sodium (B.D.H.) at the dose of 6 mg in 1 ml water, p.o., twice daily, on the same days as the steroids.

Table I lists the degree of "dyskinesia", 30 min. after LSD injection, in a scale of: 0 = no change, 1 = just detectable, 2 = mild, and 3 = maximal motor disturbances, as described elsewhere (10). However, in view of the subjectivity of such assessments, for statistical purposes, we recognized only two grades: minor and sometimes dubious degrees of dyskinesia (0 to 1 in our scale) were rated as negative, all others as positive. These data were then arranged in a 2 x 2 contingency table and the statistical significance of the apparent differences between the control and pretreated group computed by the "Exact Probability Test" of Fisher and Yates (19, 20).

Results

Our results are summarized in Table I which shows that the dyskinesia elicited by severe LSD intoxication was well prevented by PCN, CS-1, ethylestrenol, norbolethone, prednisolone, triamcinolone and estradiol, but only just significantly by progesterone and phenobarbital. The other agents tested remained without effect.

TABLE I

Effect of Various Steroids, Thyroxine and Phenobarbital on LSD Intoxication

Treatment	Dyskinesia
None	11/15
PCN	0/14 ***
CS-1	0/10 ***
Ethylestrenol	2/15 ***
Spironolactone	6/15 NS
Norbolethone	1/10 ***
Oxandrolone	5/10 NS
Prednisolone Ac.	0/10 ***
Triamcinolone	0/15 ***
Progesterone	3/10 *
Estradiol	0/10 ***
DOC-Ac.	4/8 NS
Hydroxydione	4/10 NS
Thyroxine	11/15 NS
Phenobarbital	3/10 *

NS = Not significant; * = $P<0.05$; *** = $P<0.001$

Discussion

As stated in the introduction, several earlier investigators noted that certain steroids can counteract the manifestations of LSD intoxication in various species. In general, this has been ascribed to peripheral antagonisms, possibly to interference with LSD receptor sites (7) or to the central nervous effect of such anesthetic steroids as hydroxydione (6).

Our experience throws no light on the possible effect of steroids upon LSD receptor sites. However, it is noteworthy that hydroxydione, the most potent anesthetic steroid of our series, causes no significant inhibition of LSD-induced dyskinesia, whereas estradiol - contrary to the earlier observations of Bergen et al. (9) - was maximally effective in this respect, although it is devoid of anesthetic properties.

The catatoxic steroids, which are known to be potent hepatic microsomal drug-metabolizing enzyme inducers, proved to be highly effective in antagonizing the toxicity of LSD. However, microsomal enzyme induction does not appear to be the only factor involved in this type of prophylaxis since the syntoxic glucocorticoids of our series (prednisolone and triamcinolone) were also highly efficacious, whereas phenobarbital (one of the most potent non-steroidal hepatic microsomal enzyme inducers) provided only barely significant protection against LSD.

Only extensive metabolic and neurophysiological studies could be expected to clarify the mechanism through which steroids counteract the toxicity of LSD, but it is already evident that steroids which differ widely in their hormonal and enzyme-inducing potencies can protect the rat against severe LSD intoxication.

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