Effect of Androstene Derivatives on Metacorticoid Hypertension. (20611)

F. M. STURTEVANT. (Introduced by F. J. Saunders.)

From the Division of Biological Research, G. D. Searle & Co., Chicago.

Metacorticoid, or post-DCA, hypertension is a self-sustaining cardiovascular disease attained in rats approximately 2 months after the implantation of a desoxycorticosterone acetate (DCA) pellet and the substitution of saline for drinking water(1-4). In many respects this type of hypertension appears similar to essential hypertension in man(1,5), and responds to treatment with various drugs active in the human disease(6). Metacorticoid hypertension is abolished by hypophysectomy(2) or nephrectomy(3), but not by removal of the adrenals, thyroid, parathyroids, gonads, nor by drastic dietary restriction of Na or K(1).

Materials and methods. Each experimental group consisted of 4 male Sprague-Dawley rats which had received a single 20 mg DCA pellet 3 to 6 months previously, and had been maintained on 0.86% NaCl solution and Rockland Rat Diet *ad libitum*. The systolic blood pressures of treated rats were estimated with a photoelectric tensometer(7) immediately before and 2, 4, and 5½ hours after treatment, and were compared to simultaneous readings from solvent-injected controls. The mean blood pressure of over 400 normal rats by the tensometer method has been determined as 120 mm Hg, with a standard deviation of 10. Pressure readings on individual rats were made in ignorance of the treatment the rat had received and of the previous pressure reading. Each test was completed by one person on the same tensometer in a darkened room at constant temperature. The rats were trained for at least 3 months before testing and were deprived of food and saline during the course of the experiment. The significance of the results was determined by use of the one-tailed *t*-test(8). The following compounds were injected subcutaneously in corn oil or propylene glycol in doses of 20 mg/kg: testosterone, 4-androstene-3,17-dione, 11β-hydroxytestosterone, 11β-hydroxy-4-androstene-3,17-dione, 11-ketotestosterone, and 4-androstene-3,11,17-trione (adrenosterone). These compounds represented the following derivatives of 4-androsten-3-one: 11—H and 17—OH, 11—H and 17=O, 11—OH and 17—OH, 11—OH and 17=O, 11=O and 17—OH, 11=O and 17=O, respectively.

Results. The mean blood pressures for each group of rats are listed in Table I. The most active steroid was 11-hydroxyandrostenedione; it lowered the mean blood pressure 33-49 mm Hg over a 5½-hour period. Testosterone and its 11-keto derivative lowered blood pressure 18-22 mm over the same interval. Androstenedione and adrenosterone had depressor effects of approximately 9-18 mm, while 11-hydroxytestosterone was inactive.

Discussion. By comparing the structures of these compounds with their activities, it can be concluded that replacement of the 11-hydroxyl by a hydrogen or a keto group appeared to decrease the depressor activity of the 17-ketosteroids and increase the activity of the 17-hydroxysteroids.

In rats receiving DCA, testosterone temporarily reverses the increase of blood pressure(9), partially inhibits the increase in appetite for NaCl(10), and prevents nephrosclerosis and proteinuria(11), but not cardiorenal hypertrophy(12). The "protective" effect of testosterone has been ascribed to its renotrophic activity(13).

Adrenosterone, androstenedione, 11-hydroxyandrostenedione, and 11-hydroxytestosterone have less than 5% the anabolic and androgenic effect of testosterone propionate, as measured by the increase in the weight of the levator ani muscle and seminal vesicles of castrated rats(9). Apparently the action of these steroids against metacorticoid hypertension is not explicable on the basis of their anabolic or androgenic activities.

Summary. Six derivatives of 4-androsten-3-one were tested for depressor activity in

TABLE I. Effect of Androstenes on Hypertension.

Test	Derivatives of 4-androsten-3-one	Mean group blood pressure, mm Hg: Before inj.	2 hr*	4 hr*	5½ hr*
A	11β-hydroxy-4-androstene-3,17-dione	187	153†	140‡	138†
	Propylene glycol	187	186	177	187
B	4-androstene-3,11,17-trione	186	180	169†	178†
	4-androstene-3,17-dione	184	170‡	177‡	178‡
	Corn oil	182	188	186	190
C	11β-hydroxytestosterone	180	172	182	172
	Propylene glycol	181	180	182	178
D	11-ketotestosterone	183	168	160†	160†
	Testosterone	183	161‡	162†	164†
	Corn oil	178	180	182	182

* Hr after inj.
† $P<.01$ that treat mean = control mean.
‡ $P<.05$ " " " = " " .

metacorticoid hypertensive rats. Replacement of the 11-hydroxyl by hydrogen or a keto group appeared to decrease the activity of the 17-ketosteroids and increase the activity of the 17-hydroxysteroids. The depressor activity could not be related to anabolic or androgenic activity.

The technical assistance of Catherine Tsou and Ardys Magner is gratefully acknowledged.

1. Green, D. M., Saunders, F. J., Wahlgren, N., and Craig, R. L., *Am. J. Physiol.,* 1952, v170, 94.

2. Green, D. M., Saunders, F. J., Wahlgren, N., McDonough, F. J., and Clampit, J. M., *ibid.,* 1952, v170, 107.

3. Green, D. M., Craig, R. L., Saunders, F. J., and Sturtevant, F. M., *ibid.,* 1952, v170, 477.

4. Green, D. M., Saunders, F. J., Van Arman, C. G., Calvin, L. D., and Sturtevant, F. M., *ibid.,* 1952, v170, 486.

5. Selye, H., and Horava, A., *2nd Annual Report on Stress,* Montreal, Acta, Inc., 1952, pp 22 and 228.

6. Sturtevant, F. M., PROC. SOC. EXP. BIOL. AND MED., 1953, v84, 101.

7. Kersten, H., Brosene, W. G., Jr., Ablondi, F., and Subbarow, Y., *J. Lab. and Clin. Med.,* 1947, v32, 1090.

8. Snedecor, G. W., *Statistical Methods,* Ames, Iowa State College Press, 1946, p77.

9. Saunders, F. J., unpublished data.

10. Braun-Menendez, E., *Rev. Soc. Argentina de Biol.,* 1952, v28, 23.

11. Selye, H., and Rowley, E. M., *J. Urol.,* 1944, v51, 439.

12. Friedman, S. M. and C. L., *Endocrinology,* 1950, v46, 367.

13. Selye, H., *Stress,* Montreal, Acta, Inc., 1950, p631.

Received September 22, 1953. P.S.E.B.M., 1953, v84.

Resistance Strain Gauge Arches for Direct Measurement of Heart Contractile Force in Animals.* (20612)

K. J. BONIFACE, O. J. BRODIE, AND R. P. WALTON.

From the Department of Pharmacology, Medical College of South Carolina, Charleston, S. C.

While industrial uses of resistance wire strain gauges are highly diversified, the biologic application of this device has been limited almost entirely to the recording of hydraulic pressures. Actually there are numerous biologic changes of force which can be measured advantageously by this procedure which reacts isometrically and which, with the usual instruments, is capable of frequency recordings of 100 cycles/sec. In practice, it is

* This study was supported by grants from the National Heart Institute, U. S. Public Health Service.