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Thymolytic Activity of 14α-Hydroxycortisol.* (24524)

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This communication reports thymolytic activity of 14α-hydroxycortisol by various methods in rats and mice and demonstrates that relative potency of this steroid compares to cortisol varies significantly with the thymolytic method employed.

Methods and design. Mouse thymolytic test A (Subcut. inj.). C-57 Brown female mice were obtained from Rockland Farms and bilaterally adrenalectomized and ovariectomized under ether anaesthesia at 24 days of age. The steroids were injected subcutaneously in 0.1 ml aqueous suspension in morning and afternoon one day after surgery and mice were autopsied 24 hours after first injection. Body weights and thymus weights were determined and results expressed as ratio of mg of thymus weights to grams of body weights. *Mouse thymolytic test B (Subcut. inj.).* In this test the steroids were injected once on day of operation and again on following day, all other conditions of the assay being the same as test A. *Rat thymolytic test C (Subcut. inj.).* Albino rats 25 days of age were bilaterally adrenalectomized under ether anaesthesia and injected subcutaneously once on day of surgery with 0.1 ml of Tween suspension of the steroid and again the following day. One day after last injection, the rats were autopsied, at which time thymus and body weights were determined. This injection schedule was the same as that of Mouse Test B. *Rat thymolytic test D (oral).* This test consisted in mixing the steroid with ground Purina Chow and feeding the mixture for 48 hours before determining body and thymus weights.

Results. The comparative thymolytic responses to graded doses of cortisol and 14α-hydroxycortisol using the adrenalectomized-ovariectomized mouse are presented in Table I. The statistical calculations (Table IV) demonstrate that tests A and B resulted in similar slopes, but that the index of precision was more favorable for test B and that a significantly lower potency ratio was found for the 14α-hydroxy derivative compared to cortisol. Even lower potency ratios were

TABLE I. Thymolytic Activity of 14α-Hydroxycortisol Compared to Cortisol in Adrenalectomized-Ovariectomized Mice.

Test No.	Steroid	Total dose, mg	No. of mice	Mean thymus ratio ± S.E.
A	0	0	39	3.91 ± .17
	Cortisol	.05	37	3.07 ± .12
		.1	38	3.09 ± .13
		.2	39	2.83 ± .13
		.4	38	1.87 ± .10
	14α-Hydroxy-cortisol	.05	38	3.06 ± .13
		.1	36	3.09 ± .14
		.2	36	2.55 ± .12
		.4	37	1.94 ± .11
B	0	0	18	4.54 ± .26
	Cortisol	.2	19	2.42 ± .13
		.4	20	1.24 ± .09
		.8	21	.81 ± .09
		1.6	21	.58 ± .04
	14α-Hydroxy-cortisol	.2	19	2.57 ± .19
		.4	21	2.05 ± .19
		.8	20	1.39 ± .14
		1.6	18	.75 ± .07

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TABLE II. Thymolytic Activity of 14α-Hydroxycortisol Compared to Cortisol in Adrenalectomized Rat (Test C).

Steroid	Total dose, mg	No. of mice	Mean thymus ratio ± S.E.
0	0	26	4.03 ± .15
Cortisol	.1	19	3.52 ± .13
	.2	19	3.32 ± .20
	.4	18	2.98 ± .11
	.8	18	1.98 ± .12
14α-Hydroxycortisol	.2	12	4.03 ± .19
	.4	17	3.70 ± .16
	.8	15	3.71 ± .18
	1.6	5	3.29 ± .19
	3.2	5	3.22 ± .29

TABLE III. Thymolytic Activity of 14α-Hydroxycortisol Acetate Compared to Cortisol Acetate in Adrenalectomized Rat (Test D).

Steroid	Oral dose, mg/100 g food	No. of rats	Mean thymus ratio ± S.E.
0	0	10	3.55 ± .12
Cortisol acetate	2.5	10	2.67 ± .23
	5.	9	2.00 ± .19
	10.	8	1.06 ± .19
14α-Hydroxycortisol acetate	5.	9	3.34 ± .13
	10.	9	2.95 ± .12
	20.	9	2.73 ± .24
	40.	9	1.13 ± .22

TABLE IV. Thymolytic Activity of 14α-Hydroxycortisol as Compared to Cortisol in Rat and Mouse. (Calculations by Methods of Bülbring(1) and Fischer(2).)

Test #	Species	Steroid (No. of animals)		Standard (No. of animals)		Combined slope, b_c	Index of precision, λ	Relative potency, % ± S.E.
A	Mouse	14α-Hydroxycortisol	(109)	Cortisol	(115)	−1.97	.37	109 ± 13
B	"	"	(78)	"	(81)	−2.00	.26	60 ± 6
C	Rat	"	(42)	"	(74)	−1.30	.47	12 ± 3
D	"	14α-Hydroxycortisol acetate	(36)	Cortisol acetate	(27)	−2.40	.24	19 ± 3

found when rats were used. In an assay (test C) involving subcutaneously treated adrenalectomized rats the relative potency of 14α-hydroxycortisol was 12% ± 3 (Tables II, IV). When the steroids, as acetates, were administered in the food (test D) the relative potency of the 14α-hydroxy derivative was 19% ± 3 of cortisol (Tables III, IV).

Summary and conclusion. Introduction of the 14α-hydroxy group into cortisol caused a severe reduction in thymolytic activity when assessed by a test employing the adrenalectomized rat, while similar studies in the mouse indicated a thymolytic activity of the order of cortisol. These studies demonstrate that relative activity of 2 corticoids on the thymolytic test can vary as much as 8-fold depending upon the animal and conditions chosen for the bioassay.

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