Aging and Adrenal Δ^5-3β-Hydroxysteroid Dehydrogenase in Female Rats[1] (35183)

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Adrenal steroid levels remain constant in aging (1) and the hypothalamic–pituitary–adrenal axis is normal in aged individuals (2) but the adrenal response to ACTH in cattle declines with age (3). However, there is little known regarding rodent adrenal cortical function in aging. In this regard, an increase in cellular degeneration with age suggested impaired secretory capacity (4); whereas a decline in glycogen content implied an increase in steroid metabolism (5). On the other hand, examination of urinary 17-ketosteroids (6) and adrenal ascorbic acid (7) of rats through 2 years of age indicated no change in adrenal function. A major enzyme in the steroidogenic pathway is Δ^5-3β-hydroxysteroid dehydrogenase and the enzyme is present in the rat adrenal (8). This investigation examined the effect of senescence on this enzyme in the rat adrenal.

Materials and Methods. Long-Evans strain rats, born and raised in our laboratory were used. All animals were of known birth date, were virgin females and were fed Purina fox chow supplemented weekly with cod liver oil on bread. The rats were housed in a temperature regulated room with a light–dark cycle of 12:12 hr. At various ages between 1 and 24 months, the rats were killed by decapitation at 8 to 10 a.m. Adrenals were quickly removed, weighed, and stored in dry ice until assayed within 24 hr. Δ^5-3β-Hydroxysterioid dehydrogenase (3β-OHD) was estimated biochemically (8) using dehydroepiandrosterone[2] as the substrate. Activity was reported as micrograms of androstenedione formed per minute or per milligram of protein (9). Significant differences were estimated by the Student's t test and a p value of 0.01 was considered significant.

Results. Adrenal weight increased through the first 4 months of life and thereafter remained unchanged Table I. Consequently with the increase in body weight, adrenal weight relative to body weight declined from a peak of 13.9 mg/100 g at 2 months to 9.2 mg/100 g at 24 months.

Two significant changes in 3β-OHD activity/mg of protein occurred during aging. These changes were noted at 2 months of age when enzyme activity decreased 20% but returned to a higher level at 4 months of age and again at 12 months of age when activity decreased 25% with this lower level being maintained through 24 months. Total adrenal 3β-OHD activity increased from 1 to 4 months of age as gland weight increased. Thereafter total gland enzyme activity declined. Thus total gland enzyme activity in rats 1–2 years old simulated that of a 2-month old animal of approximately half the body weight. Adrenal protein concentration increased between 1 and 2 months of age and then either declined or did not change. Total adrenal protein increased at 2 months and again at 4 months of age but did not change significantly thereafter.

Discussion. The decrease in Δ^5-3β-hydroxysteroid dehydrogenase with aging may relate to the cellular degeneration associated with aging (4) as significant reductions in enzyme activity were evident at 12 months of age. In addition, the older rat exhibits a degree of refractoriness to ACTH (10). There is also a degree of similarity between the adrenals of old rats and hypothyroid rats. Thyroidectomy caused a decrease in 3β-OHD (11) and in immature rats hypothyroidism induced with thiouracil blocked the anticipated in-

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[2] Dehydroepiandrosterone was generously supplied by Dr. Ralph Dorfman, Syntex Research, Palo Alto, California.

TABLE I. Aging and Adrenal Δ^5-3β-Hydroxysteroid Dehydrogenase.[a]

Age (months)	No. of rats	Body wt (g)	Adrenal wt (mg)	Δ^4-Androstenedione (μg/min)			Protein	
				(mg)	mg/protein	Total	(mg %)	Total
1	9	67	16.4 ± 0.6	0.335 ± 0.02	2.44 ± 0.09	5.5 ± 0.3	13.6 ± 0.2	2.2 ± 0.2
2	8	165	44.8 ± 2.0[b]	0.296 ± 0.02	2.04 ± 0.15[b]	13.6 ± 1.2[b]	14.6 ± 0.1[b]	6.7 ± 0.2[b]
4	7	246	60.0 ± 3.2[b]	0.324 ± 0.01	2.47 ± 0.11[b]	19.6 ± 1.6[b]	13.2 ± 0.2[b]	7.9 ± 0.4[b]
6	7	249	52.0 ± 4.2	0.310 ± 0.02	2.36 ± 0.12	16.3 ± 1.7	13.2 ± 0.1	6.8 ± 0.6
12	7	285	56.8 ± 2.4	0.257 ± 0.01[b]	1.84 ± 0.08[b]	14.7 ± 1.0	14.0 ± 0.4	8.0 ± 0.6
18	7	308	55.2 ± 3.8	0.251 ± 0.01	1.81 ± 0.06	13.9 ± 1.2	13.8 ± 0.1	7.7 ± 0.6
24	7	307	56.6 ± 4.8	0.233 ± 0.01	1.82 ± 0.10	13.1 ± 1.1	13.0 ± 0.4	7.4 ± 0.8

[a] Values are means ± standard error of the mean.

[b] Significantly different ($p<0.01$) from rats in the prior age group.

crease in adrenal enzyme (12). Furthermore sensitivity of the adrenal to ACTH is reduced by feeding thiouracil (13). Thus the increased incidence of hypothyroidism in senescent rats implicates the thyroid in adrenal cortical changes in aging (14).

Aging results in changes in the ovaries and estrous cycles become erratic with a presumed modification of estrogen/progesterone ratios. Older rats may exhibit either constant or prolonged estrus. The ovary of the constant estrus rat is capable of secreting unusually large amounts of estrogen (15) which may be a factor involving the adrenal since estrogens inhibit adrenal 3β-OHD (16).

Summary. Adrenal Δ^5-3β-hydroxysteroid dehydrogenase activity and protein content were determined in rats 1 to 24 months of age. Activity of the enzyme per milligram of protein declined between 6 and 12 months of age and remained low. Total gland activity was maximal at 4 months of age but declined to a level in 18–24-month-old rats that compared with the 2-month-old animal despite a marked increase in body weight.

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