Prostaglandin Dehydrogenase Activity of Rat and Rabbit Testicular Tissues and Accessory Glands before and after Castration

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Rat reproductive tissues contained both 15-hydroxy-prostaglandin dehydrogenase (PGDH) and Δ^{13}-reductase activities, while rabbit tissues exhibited only PGDH activity. In the rat, Δ^{13}-reductase activity was absent in those tissues that had a high specific activity of PGDH and was present in those tissues with a low specific activity. Total specific activity of PGDH was greatest in the testicular capsule, whereas total activity was greatest in the testicular parenchyma of both species. Total PGDH activity was highest in rat seminal vesicles, where it was second only to the testicular parenchyma. Castration significantly increased PGDH activity of the epididymis, prostate, and seminal vesicles of rats, while Δ^{13}-reductase activity disappeared from those tissues. The specific activity of PGDH was greater in the rat than in the rabbit, except for the testicular parenchyma of the rabbit. The greater PGDH activity in rat testicular capsules, compared to those of the rabbit, correlated well with diminished contractility of the rat capsule. PGDH activity of the interstitial cells correlated well with the role of prostaglandins in androgen synthesis.

Key words: prostaglandin dehydrogenase, Δ^{13}-reductase, rat and rabbit seminal vesicles, testis, epididymis, castration.

J Androl 1985; 6:97–101

Previous studies have revealed the importance of prostaglandins in normal testicular function (Hargrove et al, 1973, 1977; Ellis et al, 1978, 1981). Accessory organ function also appears to be influenced by prostaglandins (Hawkins and Labrum, 1956). At low concentrations, PGE_2 maintains normal testicular function, but at higher concentrations it inhibits spermatogenesis (Ericsson, 1973; Tso and Lacy, 1975) and decreases seminal vesicle and ventral prostate weights (Memon, 1973; 1974). Prostaglandin 15-hydroxy-dehydrogenase (PGDH) activity (PGDH—E.C. 1.1.1.141) specifically catalyzes the oxidation of the 15(S)-hydroxy group of prostaglandins. PGE, F, and A were originally detected in guinea pig lung homogenates (Anggard and Samuelsson, 1964) and PGDH activity was purified 2 years later (Anggard and Samuelsson, 1966). The oxidation of the 15(S)-hydroxy group of PGE is considered to be the initial step in the formation of almost all prostaglandin metabolites (Samuelsson et al, 1975).

Prostaglandin dehydrogenase activity has been observed in swine (Anggard et al, 1971) and rat (Nakano et al, 1971; Ellis et al, 1981; Ohuo-Obasiolu, 1982) testes, but no data exist for PGDH activity in rabbit testes or the accessory organs of any species. The present investigation was undertaken to quantify the distribution of PGDH activity in rat and rabbit testes and accessory organs, and to ascertain if there is a possible relationship of this activity to known physiologic functions (eg, testosterone synthesis or contractile activity).

Materials and Methods

Five adult (6 months old) male rabbits of mixed breeds and 12 adult male rats (Wister Strain, Simonsen Labs—250–350 g) were maintained in our small animal care facility under controlled conditions (16:8 LD photoperiod, 70 F temperature, and 35% relative humidity) with feed (rabbit pellets—Intermountain Farmers Associa-

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Submitted for publication October 10, 1983; revised version received October 15, 1984; accepted for publication November 1, 1984.

Supported by the Utah Agricultural Experiment Station project no. 454, journal paper no 2855.

tion and Lab-Blox, Wayne Pet Food Division, Continental Grain Company) and water given *ad libitum*. Six of the rats were castrated while the remaining six served as sham-operated controls. All animals were sacrificed 14 days later by decapitation and the following tissues were immediately excised and placed on ice until used in the assays: both testes, the epididymides (caput, corpus, cauda), the vas deferens, prostate glands (anterior, ventral, and posterior lobes) and seminal vesicles. Intertubular cells were isolated from rabbit testicular parenchyma by a method adapted from Epplen et al (1981). Briefly, decapsulated testes were incubated in PBS (50 mM sodium phosphate in 8.5 g/l NaCl) *p*H 7.2, containing 1 mg/ml of collagenase III and 0.04 mg/ml of DNase (Sigma Chemical Company) (2 ml/testis) for 30 minutes at 28 C in a shaking water bath (Labline).

Partially-freed seminiferous tubules were teased free of the testicular parenchymal mass with forceps. All of the freed tubules were then transferred to pre-weighed test tubes on ice. To harvest the cells, the freed intertubular cells, suspended in the incubation media, were transferred to pre-weighed centrifuge tubes, and were centrifuged at 300 × g for 10 minutes at 0.5 C. The weights of the seminiferous tubules and intertubular cells were quantified to the nearest 0.01 g after centrifugation and removal of the incubation media. The epididymides were freed from adhering adipose and connective tissue and were separated into caput, corpus, and cauda portions.

The various cellular fractions were assayed for PGDH activity as described elsewhere (Ellis and Jorgensen, 1982; Ohuo-Obasiolu et al, 1982) with modifications as described below. Aliquots of each tissue or cellular fraction were homogenized in Bücher's medium (1:7 w/v) in an all-glass (Duall-Kontes) tissue grinder over ice. The resulting homogenate was centrifuged for 15 minutes at 15,000 × g at 1 C in a preparative ultracentrifuge (Beckman Model L). The incubation mixture consisted of 250 µl of the supernatant solution, 250 µl of Bücher's media containing 1.66 mg of NAD and 10 µl (1.25 mmol of a stock solution (0.5 µCi) of radioactively labeled [^{3}H]PGE$_2$, [5,6,8,11,12,14,15-^{3}H(N)]-PGE$_2$ (New England Nuclear). After 30 minutes of incubation at 37 C, the reaction was terminated by adding 65 µl of 1 N HCl. The radioactively labeled prostaglandin substrate and its metabolites were quantitatively extracted from the incubation media using 3 1-ml aliquots of distilled ethyl acetate. The extracts were transferred to 15-ml conical centrifuge tubes, evaporated to dryness with dry N_2 gas, and concentrated in the tips of the test tubes by rinsing the walls of the tubes three times with ethyl acetate. The residues were dissolved in 3 drops of chloroform:methanol (1:1 v/v) and were quantitatively transferred to 3-cm wide strips of chromatofilm (Eastman Chromatogram 13179 silica gel sheets) with two more additions of 3 drops of solvent dropped onto the lower walls of the tubes, with hand mixing to ensure quantitative transfer. The loaded strips were subjected to ascending thin-layer chromatography using ethyl acetate:acetic acid:isooctane:water (110:20:50:100 v/v/v/v) as the solvent system. The radioactivity was localized on the chromatograms with a 2π Geiger–Muller electronic autoscanner (Nuclear Chicago Actigraph III). The radioactive areas on the chromatograms corresponding with authentic carrier 15-keto-13,14-dihydro-PGE$_2$ (The Upjohn Company) were cut out, placed in scintillation vials with 10 ml of scintillation cocktail, and counted for 10 minutes in a liquid scintillation spectrometer (Packard Instruments Company, model 527).

The data were expressed as the amount of 15-keto-PGE$_2$, and 15-keto-13,14-dihydro-PGE$_2$ formed and total PGDH activity (the sum of both metabolites). The data were evaluated statistically using an F-test (2 × 3 factorial with an interaction term) to determine overall differences, followed by a multiple means comparison test (Ostle and Mensing, 1975) to compare individual differences.

Results

Rat

Both PGDH (the formation of 15-keto-PGE$_2$) and Δ^{13}-PG reductase (the formation of 15-keto-13,14-dihydro-PGE$_2$) activities were detected in all rat reproductive tissues studied (Table 1) except the caput and cauda epididymides, and the ventral and posterior lobes of the prostate gland, where only PGDH activity was observed. The anterior prostate lobe of the rat had over 1.2 times higher total PGDH specific activity than did either the ventral or posterior lobes, while total PGDH activity on a per animal basis was higher in the ventral and posterior lobes than it was in the anterior lobe. Total PGDH activity of the seminal vesicles on a per animal basis was high compared to the other tissues, and was second only to the testicular parenchyma, where there was a much greater mass. Δ^{13}-reductase activity was present only in those tissues with a low specific activity of PGDH activity.

Castration of adult male rats significantly reduced assessory organ weights, but not the weight of the ductus deferens (Table 2). Total specific activity of PGDH was significantly ($P < 0.001$) increased by castration in the caput, corpus, and cauda epididymides (2.9, 3.1, and 2.7 times, respectively) (compare data in Table 1 with Table 3). Similar increases were also observed for the prostate and seminal vesicle glands, despite significant decreases in the weights of these organs. After castration, total activity on a per animal basis (compare Table 1 with Table 3) was decreased in the caput epididymides ($P < 0.05$), increased in the corpus epididymidis ($P < 0.01$), decreased in the cauda epididymidis ($P < 0.05$), increased in the ventral prostate ($P < 0.01$), decreased in the seminal vesicles ($P < 0.01$), and was unchanged in the vas deferens. Thus, with the exception of the prostate gland and vas deferens, if the weight loss was 65% or greater, there was a decrease in total PGDH

TABLE 1. Normal Rat PGDH Activity of Testicular Components, Vas Deferens, Prostate and Caput, Corpus and Cauda Epididymidis*

Cell Fraction	Specific Activity Basis × 10^5			Per Animal Basis × 10^5		
	PGDH Activity† cpm/g Tissue	Δ^{13}-Reductase Activity‡ cpm/g Tissue	Total PGDH Activity§ cpm/g Tissue	PGDH Activity cpm/Animal	Δ^{13}-Reductase Activity cpm/Animal	Total PGDH Activity§ cpm/Animal
Testis capsule	2.55 ± 0.24	14.24 ± 2.41	16.8 ± 1.43	0.27 ± 0.02	1.5 ± 0.25	1.76 ± 0.14
Testis parenchyma	0.03 ± 0.02	8.1 ± 0.49	8.14 ± 0.25	0.83 ± 0.06	19.78 ± 1.18	20.61 ± 0.62
Caput epididymidis	16.3 ± 0.14	—	16.3 ± 0.14	4.68 ± 0.04	—	4.68 ± 0.04
Corpus epididymidis	1.53 ± 0.79	6.27 ± 0.04	7.8 ± 0.61	0.16 ± 0.08	0.66 ± 0.0	0.82 ± 0.04
Cauda epididymidis	11.91 ± 0.11	—	11.91 ± 0.11	4.76 ± 0.05	—	4.76 ± 0.05
Anterior prostate	4.68 ± 0.38	6.38 ± 0.37	11.06 ± 0.38	0.46 ± 0.04	0.63 ± 0.04	1.08 ± 0.04
Ventral prostate	6.89 ± 0.23	—	6.89 ± 0.23	2.02 ± 0.07	—	2.02 ± 0.07
Posterior prostate	6.64 ± 0.29	—	6.64 ± 0.29	2.59 ± 0.02	—	2.59 ± 0.02
Seminal vesicle	4.56 ± 0.41	6.44 ± 0.33	11.01 ± 0.37	3.95 ± 0.29	4.59 ± 0.24	8.54 ± 0.26
Vas deferens	0.11 ± 0.04	2.28 ± 0.82	2.39 ± 0.43	0.02 ± 0.01	0.34 ± 0.12	0.36 ± 0.07

* Mean ± SEM.
† Measured as the amount of ^{3}H-15-keto-PGE$_2$ formed from ^{3}H-PGE$_2$.
‡ Measured as the amount of ^{3}H-15-keto-13,14-dihydro-PGE$_2$ formed from ^{3}H-15-keto-PGE$_2$.
§ Obtained by adding the two above values, that is, PGDH and Δ^{13}-reductase activities.

activity on a per animal basis, but if the weight loss was 46% or less, activity increased. Castration also resulted in the disappearance of measurable Δ^{13}-prostaglandin reductase activity from those tissues exhibiting activity in intact animals (data not shown).

Rabbit

In the rabbit, the only appreciable enzyme activity found (Table 4) was PGDH (ie, 15-keto-PGE$_2$ was the only metabolite found on the chromatograms—data not shown). Δ^{13}-reductase activity was absent in those tissues that had a high specific activity of PGDH (above 600,000 cpm/g tissue). Total specific activity of PGDH was greatest in the capsule, whereas the highest total activity (on a per animal basis) was observed in the parenchyma, due to the greater mass of cells (Table 4). In the epididymis, the greatest specific activity was observed in the corpus, followed by caput and cauda epididymides, respectively, where, on a per animal basis, the greatest total activity was also observed.

Species Comparisons

The specific activities for total PGDH in the rat reproductive tissues were greater (compare Tables 1 and 3) than those of the rabbit with the exception of the rabbit parenchyma ($P < 0.005$). Total PGDH activity, expressed on a per animal basis for the

TABLE 2. Testicular and Accessory Organ Weights of Control and Castrate Male Rats and Male Rabbits

Tissue	Rats (12 per group)		Weight Differences		Rabbits (5 per group)
	Control (g)	Castrated† (g)	(g)	(%)	Control (g)
Testicular capsule	0.10 ± 0.01*	—			0.50 ± 0.04
Tubular cells	—	—			2.75 ± 0.02
Inter-tubular cells	—	—			0.77 ± 0.01
Parenchyma	2.44 ± 0.05	—			3.09 ± 0.01
Caput epididymis	0.29 ± 0.01	0.09 ± 0.01‡	0.20	69.0	0.44 ± 0.01
Corpus epididymis	0.10 ± 0.01	0.06 ± 0.01‡	0.04	40.0	0.16 ± 0.01
Cauda epididymis	0.40 ± 0.01	0.14 ± 0.02‡	0.26	65.0	0.57 ± 0.07
Anterior prostate	0.10 ± 0.01	—			—
Ventral prostate	0.29 ± 0.01	—			—
Posterior prostate	0.39 ± 0.01	—			—
Total prostate	0.68 ± 0.01	0.22 ± 0.03‡	0.46	67.6	0.62 ± 0.01
Seminal vesicle	0.71 ± 0.02	0.13 ± 0.01‡	0.58	81.7	0.22 ± 0.06
Vas deferens	0.15 ± 0.01	0.12 ± 0.02	0.03	20.0	0.25 ± 0.09

* Mean values ± SEM.
† Rats were castrated 14 days before being sacrificed.
‡ $P < 0.01$ when compared with control rats.

TABLE 3. Total PGDH Activity Measured as PGDH and 15-keto-PG-Δ^{13}-reductase Activities in the Epididymides and Accessory Organs of Male Rats 14 Days after Castration*

Tissue	Specific Activity cpm/g Tissue × 10^5	Total Activity cpm/Both Testes × 10^5
Caput epididymidis	47.62 ± 1.13	4.43 ± 0.11
Corpus epididymidis	24.39 ± 5.31	1.54 ± 0.33
Cauda epididymidis	32.25 ± 0.72	4.52 ± 0.10
Prostate gland	24.06 ± 5.11	5.17 ± 1.10
Seminal vesicle	44.35 ± 1.02	5.59 ± 0.13
Vas deferens	3.78 ± 0.31	0.47 ± 0.04

* Mean ± SEM.

various reproductive tissues, was greater for the rabbit than for the rat, due to the greater testicular mass in the rabbit. In rabbits, as in rats (Tables 1 and 3), the greatest total specific activity was observed in the capsule rather than the parenchyma or seminiferous tubules. The fact that the sum of specific activity in the seminiferous tubules plus the intertubular cells does not equal the activity of the testicular parenchyma indicates that some PGDH enzyme activity was lost during incubation with collagenase. Of interest is the higher specific activity of total PGDH activity in the intertubular cells when compared with the seminiferous tubules.

The corpus epididymidis had a higher specific activity of PGDH than did the caput, which, in turn, had a greater activity than did the cauda epididymidis ($P < 0.001$).

Discussion

PGDH and Δ^{13}-reductase activities of rat and swine testes are exceeded in activity by only the kidney (Anggard et al, 1971; Nankano et al, 1971). It is generally concluded that prostaglandins are first oxidized in the C-15 position to form the 15-keto-derivative, which can subsequently be reduced in the C-13 position to form the 15-keto-13-dihydro-derivative (Anggard et al, 1971; Nankano et al, 1971; Pace-Asciac, 1975; Pace-Asciac and Miller, 1973; Sun and Armour, 1974; Ellis and Jorgensen, 1982; Ohuo-Obasiolu et al, 1982). Since 15-keto-13-dihydro PGE_2 is formed from 15-keto-13-dihydro PGE_2 in male reproductive tissues (Ellis and Jorgensen, 1982), 15-keto-13-dihydro PGE_2 formation also represents part of the total PGDH activity. Therefore, total PGDH activity as used in this investigation represents the sum of these two metabolites. Moreover, all of the above workers have expressed their data in this manner (ie, they have expressed their data as PGDH, Δ^{13}-reductase and total PGDH activities). Δ^{13}-reductase activity is of importance since 15-keto-prostaglandins have been reported as having considerable biologic activity (Dawson et al, 1974). The data in this investigation have been expressed as specific activity (cpm/mg of tissue) to ascertain if the enzyme activity decreases at the same rate as cellular activity after castration. Total activity on a per animal basis reflects the maximal ability of the tissue to metabolize prostaglandins and takes total cellular mass into account.

The present finding that the greatest total specific activity of PGDH existed in the testicular capsule of both the rat and the rabbit is consistent with the observed role of prostaglandins in initiating rabbit testicular capsular contractions (Hargrove et al, 1973; Nemetallah et al, 1983). The higher specific activity of PGDH in the rat compared to the rabbit capsule could partially explain why the rat capsule, unlike that of the rabbit and of most other species, does not exhibit spontaneous rhythmic capsular contractions (for recent reviews see Ellis et al, 1978; 1981). The higher total specific PGDH activity in the capsule of the rat and rabbit, when compared to the testicular parenchyma for PGE_2 activity, is consistent with similar observations in the rat testes for PGE_1 (Ohuo-Obasiolu et al, 1982).

It is likely that the high levels of PGDH activity in the interstitial cells are related to the synthesis and metabolism of prostaglandins as part of the mechanism of LH action on these cells in androgen synthesis (Bartke, 1969; 1971). Previous findings

TABLE 4. Total PGDH Activity Measured as PGDH and 15-keto-13,14-dihydro-PGE_2 in Intact Testicular Tissues, Accessory Organs, and Excurrent Ducts of the Rabbit Reproductive Tract*

Tissue	Specific Activity cpm/g Tissue† × 10^5	Total Activity cpm/Animal† × 10^5
Testis capsule‡	9.88 ± 0.29[a]	4.94 ± 0.14[a]
Seminiferous tubules	0.52 ± 0.15[b]	1.44 ± 0.42[b]
Intertubular cells	1.75 ± 0.16[c]	1.34 ± 0.13[c]
Testicular parenchyma	20.11 ± 0.18[d]	62.06 ± 0.55[d]
Caput epididymidis	1.01 ± 0.18[e]	0.45 ± 0.08[e]
Corpus epididymidis	2.18 ± 0.13[f]	0.34 ± 0.02[e,f]
Cauda epididymidis	0.42 ± 0.09[b,h]	0.24 ± 0.05[f]
Vas deferens	1.06 ± 0.32[e]	0.26 ± 0.08
Prostate gland	0.13 ± 0.04[g]	0.08 ± 0.03[g]
Seminal vesicle	0.29 ± 0.04[h]	0.06 ± 0.01[g]

* Mean ± SEM.

† Mean values with differing superscripts differ significantly from each other.

‡ Five animals per group.

that the prostaglandin content of the rat cauda epididymidis is four times higher than that in the caput epididymidis (Gerozissis and Dray, 1977) are consistent with our observation that PGDH activity of the caput region is significantly higher than that of the cauda epididymides of both the rabbit and rat. In this respect, when spermatozoa are flushed from the epididymis, PGDH activity is reduced by approximately 50% (unpublished observations from this laboratory). Moreover, Badr et al (1975) provided evidence that prostaglandins in the epididymis are sequestered in the luminal contents. They also showed that the vas deferens contained significantly higher concentrations of PGEs and PGFs than were found in the epididymis or the seminal vesicle. The increase in specific activity of total PGDH activity in the caput and corpus epididymidis and seminal vesicles after castration indicates that PGDH activity is not lost as fast as was cellular mass. The variable percent loss of accessory organ weights and variable changes of total PGDH activities on a per animal basis suggest that the control of PGDH activity and the cellular activity of these glands are complicated. The fact that PGDH activity of rat testes is hormonally controlled (Ohuo-Obasciolu et al, 1982) underlines the importance of ascertaining hormonal influences on the activity of this enzyme in the accessory organs.

Acknowledgments

We thank Dr. Azza Nemetallah for her technical assistance.

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