The Seoul Journal of Medicine
Vol. 26, No. 4:309-317, December 1985

Effect of Zinc on Androgen Metabolism in the Rat Ventral Prostate*

Chongwook Lee, Chan-Woong Park, Sang-Goo Shin and Dong-Keun Song

Department of Pharmacology, College of Medicine, Seoul National University, Seoul 110, Korea

= Abstract =The *in vitro* effect of zinc on the metabolism of androgen was examined to identify the role of zinc on the regulation of dihydrotestosterone level in the prostate. The activities of 5 α -reductase and 3 α -hydroxysteroid oxidoreductase were assayed in the homogenate of the rat ventral prostate with (^{3}H)-testosterone or (^{3}H)-dihydrotestosterone as a substrate in the presence of 5 x 10^{-4} M NADPH. The zinc content of normal rat ventral prostate measured by atomic absorption spectroscopy was 29.92 $\pm$ 5.56 μg per gm tissue of wet weight.

The Km and Vmax values of 5-reductase were 353.5 $\pm$ 32.3 nM and 41.8 $\pm$ 1.1 pmole/30 min/mg protein respectively and of 3 α -hydroxysteroid oxidoreductase were 1477.2 $\pm$ 177.4 nM and 823.2 $\pm$ 81.7 pmole/30 min/mg protein. Zinc inhibited both enzymes in a non-competitive manner respecting to the substrate. The half inhibition concentration of zinc on 5 α -reductase and 3 α -hydroxy-steroid oxidoreductase were 18.3 $\pm$ 5.2 and 97.4 $\pm$ 33.0 μM respectively.

From this experiment it was suggested that zinc might play an important role on the regulation of dihydro-testosterone level in the prostate by influencing the activities of 5 α -reductase and 3 α -hydroxysteroid oxidoreductase.

Key Words: ***Zinc, Androgen metabolism, Ventral prostate, Rat***

INTRODUCTION

Androgen is essential for normal development and maintenance of function of the prostate. Although the mechanisms of androgen utilization by prostatic tissues are incompletely known, some of their metabolic processes are relatively well delineated. Plasma testosterone passes through the prostatic cell membrane into the cytoplasm, where it is converted to dihydrotestosterone-(DHT), which is a more potent androgen than testosterone itself, by Δ^4-3-oxosteroid reductase (5 α -reductase). DHT binds to a specific cytoplasmic receptor protein. This complex is then translocated into the nucleus where it binds to the DNA of nuclear chromatin and activates the DNA to produce messenger RNA. DHT is further metabolized mostly by 3 α (β)-hydroxysteroid oxidoreductase(3 α (β)HSO) in the cytoplasm (Bruchovsky & Wilson 1968; Mainwaring 1977; Ghanadian & Smith 1983).

The association of the concentration of DHT in the prostatic tissue with the activity of 5 α -reductase has been widely investigated. There are several reports that the concentration of DHT in the prostate is 3~4 fold higher in the benign prostatic hyperplasia (BPH) than in the normal prostate (Geller *et al.*, 1976; Habib *et al.* 1976; Hammond 1978). Increased activity of 5 α -reductase in BPH was found (Bruchovsky & Lieskovsky 1979) and decreased activity of the same enzyme in the prostatic cancer (Prout *et al.* 1976).

Zinc is an important trace element which is a normal constituent of many enzymes and proteins and is involved in the growth and development of many organs (Vallee 1959). Zinc content of the human prostate is known to be high (Bertrand & Vladesco 1921) and zinc concentration in the pros-

* This study was supported by the research grant 1985 of Ministry of Education, Republic of Korea.

tate is approximately 10 times higher than in other soft tissue (Mawson & Fischer 1952). The zinc concentration of the prostate is decreased by estrogen or castration and is increased by testosterone (Prout *et al.* 1959). Lo *et al.* (1960) demonstrated that the epithelial cells of the canine prostate are damaged by zinc chelating agent, diphenyl-thiocarbazone (dithizone). The concentrations of zinc in the prostate are variable in the BPH (Schrodt *et al.* 1964; Gyorkey *et al.* 1967; Feustel *et al.* 1982) and are significantly lower in the carcinoma of the prostate than in normal control (Gyorkey *et al.* 1967; Habib *et al.* 1980; Feustel *et al.* 1982). Although the role of zinc in the prostate remains unexplained, zinc might be closely associated with many physiological functions and the pathophysiology of the prostate (Habib 1978).

The concentrations of zinc in the prostate appeared to be closely associated with the metabolism of testosterone in the prostate. Recently, Leake *et al.* (1984a) emphasized that zinc modulates testosterone metabolism by enhancing the 5 α-reductase activity in the low concentration or by suppressing the 5 α-reductase activity in the high concentration. However, prostatic levels of DHT depend on the activities of both 5 α-reductase and 3 α-hydroxysteroid oxidoreductase. The authors are interested in the relations which may exist between prostatic zinc levels and prostatic androgen metabolizing activities. We investigated the characteristics of 5 α-reductase as well as 3 α (β) HSO and the effects of zinc on these metabolizing activities.

MATERIALS AND METHODS

1. Chemicals: (1,2-^{3}H) Testosterone (specific activity; 60 Ci/mmol), 5 α-dihydro (1,2,-^{3}H) testosterone (specific activity; 54 Ci/mmol) were obtained from Amersham. The vehicle was dried under nitrogen flow, reconstituted in ethanol and were diluted in Tris buffer solution (pH 7.0). Nonradioactive testosterone products were obtained from Sigma, and other reagents were obtained from Sigma and Merck Co.. All the buffer solutions and reagents were prepared with distilled water treated by Chelex 100 ion-exchange resin.

2. Source of Tissue: From male Sprague-Dawley rats, weighing about 200 gm, the ventral prostate from each rat was dissected free of its capsule.

3. Measurement of Zinc Content of the Prostate: Tissue (100 mg of ventral prostate) was digested for 30 min with 1.5 ml of concentrated nitric acid in the 70°C water bath. Measurement of zinc were carried out with a Pye Unicam model SP 1,900 Atomic Absorption Spectrophotometer at 213.8 nm. Zinc concentration in the prostate was expressed in μg/gm wet tissue.

4. Preparation of Homogenates: Three mililiters of homogenizing solution (5 mM $MgCl_2$, 50 mM NaCl, 0.5 mM mercaptoethanol, 10 mM Tris buffer solution, pH 7.0) was added to 100 mg of prostate tissue and aliquots were homogenized three times using a Polytron tissue breaker (Brinkman Instruments) for 15 seconds with a 30 second interval at a setting of rheostat 5. The homogenate was filtered through 2 layers of gauze and filtrate was homogenized by glass-teflon homogenizer. Protein concentrations in homogenates were measured by the Lowry method (1951). All the procedures were done at 0-4°C.

5. Conditions for Measurement of Enzyme Activities: Ten nM testosterone containing 3.3 nM (1,2-^{3}H)testosterone (0.2 μCi) or 35 nM dihydrotestosterone containing 3.7 nM 5 α-dihydro (1,2-^{3}H)testosterone (0.2 μCi) for 5 α-reductase or 3 α-hydroxysteroid oxidoreductase activity measurement respectively was added to the reaction medium (final volume of 1 ml) containing 5 mM $MgCl_2$, 50mM NaCl, 0.5 mM mercaptoethanol, 10 mM Tris (pH 7.0), 5 X 10^{-4}MNADPH and 500 μg protein of the prostate homogenate. After incubation at 37°C water bath for 3 minutes, reaction was begun with an addition of substrate and after 30 minutes the reactions were stopped with 5 ml of chloroform : methanol (2:1, V/V).

Influence of zinc concentration on the enzyme activities were monitored by either the depletion of zinc to zero by 1 mM EDTA or the addition of various amounts of $ZnCl_2$ to the prostate homogenates.

6. Extraction of Testosterone and Its Metabolites: The reaction mixture was shaken with a rotary shaker at 500 rev/min for 20 minutes, it was centrifuged at 400 xg for 10 minutes. The upper aqueous phase was discarded. After the chloroform layer was washed with 1.5 ml of chloroform:methanol water (3 : 48 : 47), the chloroform layer was dried under nitrogen flow. For the measurement of 5 α-reductase activity, 25 μg each of testosterone, DHT, 3 α-androstane-3 β-, 17 β-diol(3 β-diol), androsterone, 5 α androstanedione, and for the measurement of 3 α-HSO activity, DHT, 3 α-diol, 3 β-diol, androsterone, 5 α-androstanedione were added as standards. Fifty microliters of the sample were transferred to the

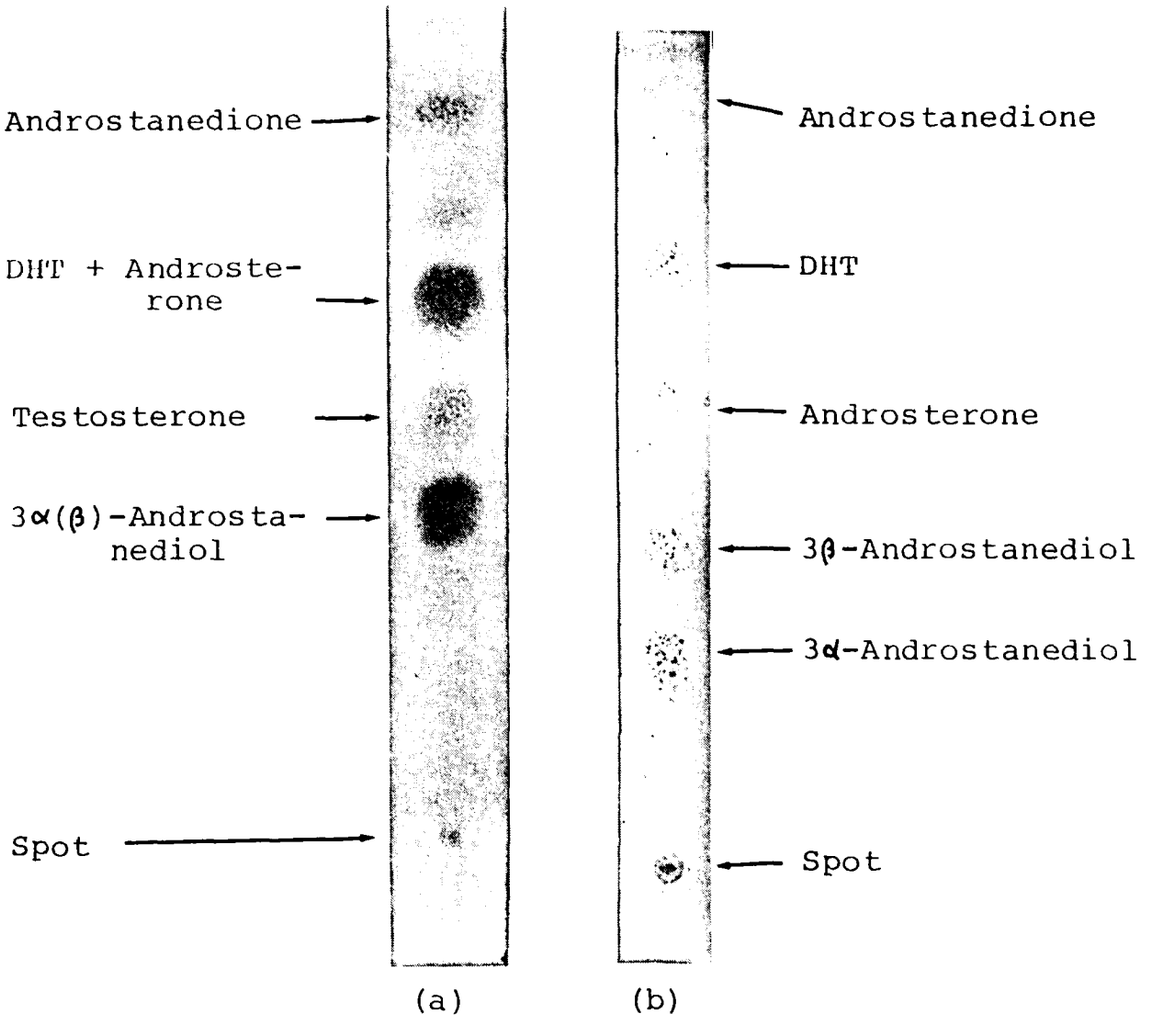

Fig. 1. TLC separation of testosterone metabolites on silica gel G(a) and Aluminium oxide(b) plate.

TLC plate.

7. **Thin Layer Chromatography of Testosterone and Its Metabolites**: For the separation of testesterone metabolites, spotted silica gel G plates were developed in benzene:ethanol (96 : 4) and were dried at room temperature. The plates were redeveloped in benzene:ethanol(9 : 1), and were sprayed with sulfuric acid (15%, v/v) in ethanol, then they were heated in an oven for 5 to 10 minutes at 100°C. 3α-diol, 3β-diol, testosterone, DHT, androsterone and androstanedione were separated (Fig. 1a). For the separation of DHT metabolites, Aluminum Oxide F254 neutral (type T) TLC aluminum sheet (Merck) was used. After The spotted Plates were developed in dichloromethane: ether (9 : 1) and dried at room temperature and then redeveloped in the same solvent system, 3α-diol, 3β-diol, DHT, androsterone and andros-

Table 1. Summary of steroid substrates, assay conditions, and metabolites to determine the activities of 5α-reductase and 3α-hydroxysteroid oxidoreductase

Enzymatic Activity assayed	Substrates (nM)	Assay conditions (μg tissue; min of incubation)	Metabolites to calculate enzyme activity				
			3β17β-diol	3α17β-diol	3α-ol 17-one	17β-ol 3-one	3,17-dione
5α-Reductase	Testosterone (10)	500 ; 30	+	+	+	+	+
3α-Hydroxysteroid oxidoreductase	Dihydrotesto-sterone(35)	500 ; 30	−	+	+	−	−

Table 2. Conversion characteristics of testosterone and dihydrotestosterone by homogenates of the rat ventral prostate

Substrate			
Testosterone		Dihydrotestosterone	
Testosterone remaining	90.32±0.94(%)	DHT remaining	49.69±4.95(%)
DHT+Androsterone	6.14±1.11	3α-androstanediol	46.96±5.05
3α(β)-Androstanediol	3.37±0.45	3β-androstanediol	0.92±0.007
Androstanedione	0.16±0.07	Androsterone	1.70±0.09
		Androstanedione	0.72±0.16

Each value represents mean±S.E. of 10 experiments.

tanedione were separated (Fig. Ib).

8. Calculation of Enzymic Activities: After each fraction of TLC Plate was separated, mixed with 15ml of liquid scintillation cocktail [0.4% diphenyloxazole in toluene: methanol (10 : 1)], The radioactivity was measured by a Beckman LS 8,800 liquid scintillation counter. The counting efficiency was determined by the external standard.

5α-reductase activity was determined by the conversion rate of testosterone to 3α-diol, 3β-diol, androsterone, DHT, androstandion and 3α-HSO activity by the conversion rate of DHT to 3α-diol and androsterone and values were expressed as pmol/30min/mg protein (Table 1).

The activity of each enzyme was determined in the presence of 1 mM EDTA and the conversion rate of substrate to each metabolite was as in Table 2. Main product by 5α-reductase was DHT and 3α-diol and that of 3α- was 3α-diol. The amount of converted 3β-diol by 3α-HSO was so negligible that it was ignored.

RESULTS

1. Property of 5α-Reductase and 3α-HSO of the Ventral Prostate: The enzyme activities were continuously increased even at the higher concentration than the normal steroid concentrations of the prostate, when concentrations of testosterone or DHT were varied up to 200- 300 nM with a reaction time for 30 minutes. Activitis of 3α-HSO was 5.5~8.1 times higher than that of 5α-reductase in all ranges of various substrate concentrations (Fig 2a, 2b).

2. Zinc Content of Ventral Prostate: The average weight of the rat ventral prostate was 129.3± 18 (S.E) mg and the average zinc content per gram of the ventral prostatic tissue was 29.92 ± 5.56 (S.E) μg. Zinc content in the reaction medium by adding tissue homogenate was estimated to be 2.3 $\times 10^{-7}$ M without EDTA(Table 3).

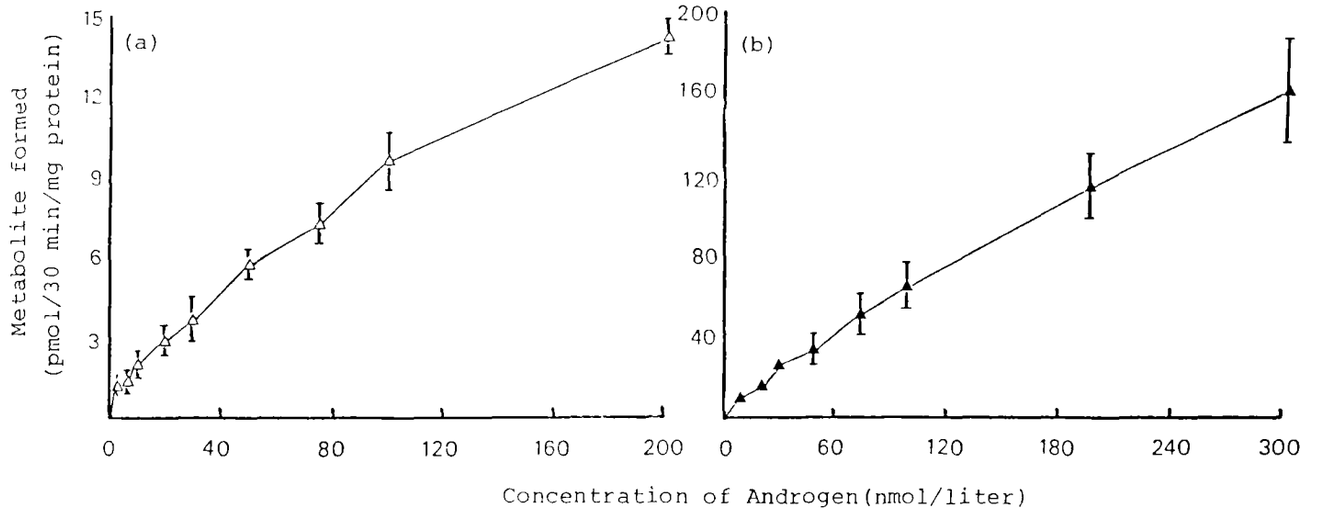

Fig. 2. Effect of concentration of androgen on the rate of metabolism by 5α-reductase(a) and 3α-hydroxysteroid oxidoreductase (b) in homogenates of rat ventral prostate. Each bar represents the standard error of mean of 5 experiments.

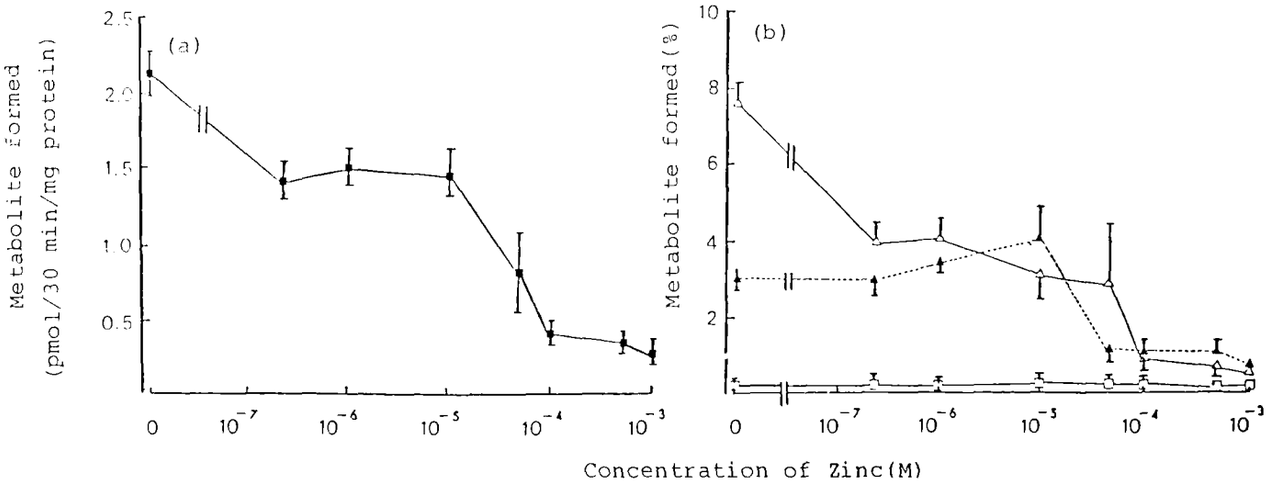

Fig. 3. Effect of zinc on the activity of 5α-reductase(a) in homogenates of rat ventral prostate. Mean conversion percent of testosterone to individual metabolite are plotted(b). Each bar represents the standard error of mean of 5 experiments. (△) DHT+androsterone; (▲) 3α(β)-androstanediol; (□) androstanedione.

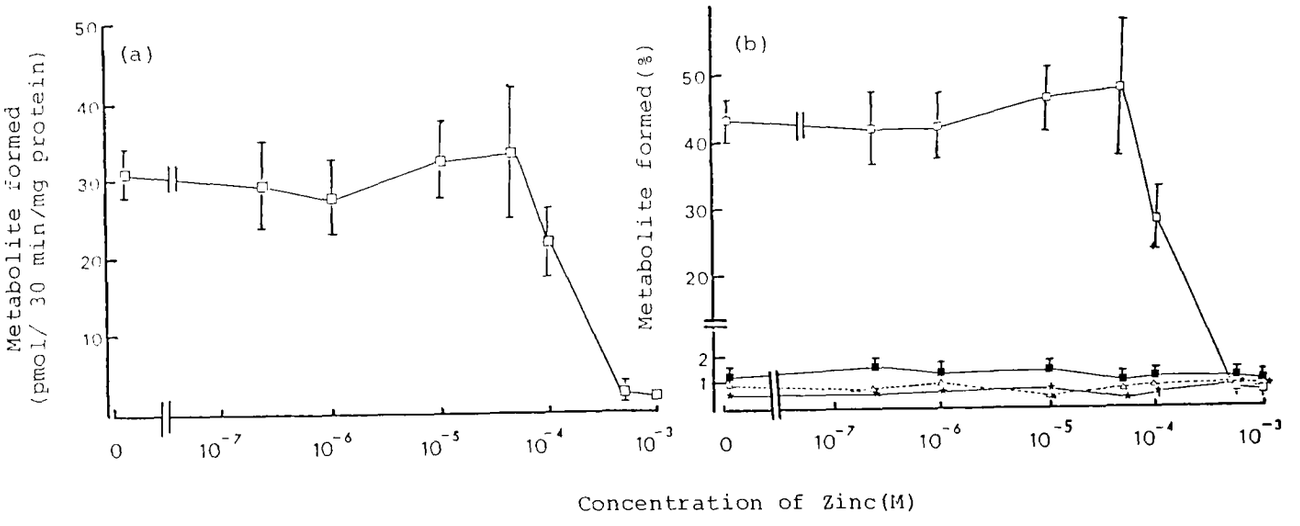

Fig. 4. Effect of zinc on the activity of 3α-hydroxysteroid oxidoreductase(a) in homogenates of rat ventral prostate. Mean conversion percents of dihydrotestosterone to individual metabolite are plotted(b). Each bar represents the standard error of mean of 5 experiments. (□) 3α-androstanediol; (■) androsterone; (△) androstanedione; (·) 3β-androstanediol.

Table 3. Zinc content of rat ventral prostate (Mean±S.E.)

No. of Animals	Body weight	Wet wt. of ventral prostate	Zinc content
5	201±21.9 g	129.3±18.0 mg	29.9±5.6 μg/g

3. Effect of Zinc on the Activities of 5α-Reductase and 3α-HSO: The activity of 5α-reductase was 2.11 ± 0.14 (S.E) pmol/30min./mg protein when 1 mM of EDTA was added, which was significantly higher than 1.42 ± 0.09 (S.E) pmol/30 min./mg protein without addition of EDTA. The enzymic activity was not changed between 2.3×10^{-7}M and 1×10^{-5} M concentrations, but was abruptly decreased at 1×10^{-4} M where the activity showed 81% inhibition comparing with the value of EDTA treated. The activity was inhibited by 86% at 1 mM zinc concentration(Fig. 3a).

The degree of conversion to each metabolites according to various concentration of zinc was as in Fig 3b. The activity of 3α-HSO was 31.0 ± 2.40 (S.E.) pmol/30 min./mg protein when 1 mM of EDTA was added, which was not different from 29.33 ± 5.05 (S.E) pmol/30 min/mg protein without addition of DETA. There was no evidence of inhibition of the enzyme activity by increasing concentrations of zinc up to 5×10^{-5} M. The enzyme activity decreased significantly at higher concentration than 5×10^{-5} M. The percentage of inhibition of the activities at 5×10^{-4} M and 1 mM were 91% and 93%, respectively (Fig. 4a). The degree of conversion to each metabolites according to various concentration of zinc was as in Fig 4b.

4. The Kinetics of Inhibition of 5α-Reductase and 3α-HSO Activities by Zinc: 5α-Reductase activities were assayed in various concentrations of substrate with the presence of zinc at the concentration from 2×10^{-5} to 3×10^{-5} M to analyze the effect of zinc on the enzyme kinetics. The kinetic parameters were calculated by Michaelis-Menten equation with a method of least square computer fit.

The average Km and Vmax values of 5α-reductase were 353.5± 32.3 (S.E.) nm and 41.8±1.1 pmol/30 min./mg protein, respectively. Hill's coefficient was 0.83±0.003 suggesting that substrate and enzyme were interacted with a 1:1 ratio. The average Km value with the addition of zinc was 372.7±7.2 mM which showed no significant difference from control Km valaue. The Vmax value in the presence of 2×10^{-5} M to 3×10^{-5} M of zinc was 12.53 to 20.81 pmol/30 min./mg protein which was significantly lower than control($p<0.005$). This appeared to be a feature of non-competitive inhibition and Ki was $1.83\pm0.52\times10^{-5}$ M and Hill's coefficient in the presence of zinc was 1.05±0.02.

The Lineweaver-Burk Plot of the zinc inhibition of 5α-reductase was as Fig 5.

Inhibition of 3α-HSO by zinc was analyzed at zinc concentration of $2\sim3\times10^{-4}$ M. The average Km value was 1,477.2±177.4 (S.E.) nM in control and 1,187±64.2 nM in the presence of zinc, there was no significant difference between two groups. The Vmax value in the presence of 2×10^{-4} to 3×10^{-4} M of zinc was 103.63 to 516.17 pmol/30 min/mg protein which was significantly lower than the control value of 823.2±81.7 (S.E.) pmol/30min./mg protein($p<0.005$). This appeared to be a feature of non-competitive inhibition and Ki, half-inhibition concentration of zinc was $9.74\pm3.30\times10^{-5}$ M, which was a much higher concentration than in case of 5α-reductase. Hill's coefficient in the control and in presence of zinc was 1.01±0.03 and 1.02±0.01, respectively, and there was no dif-

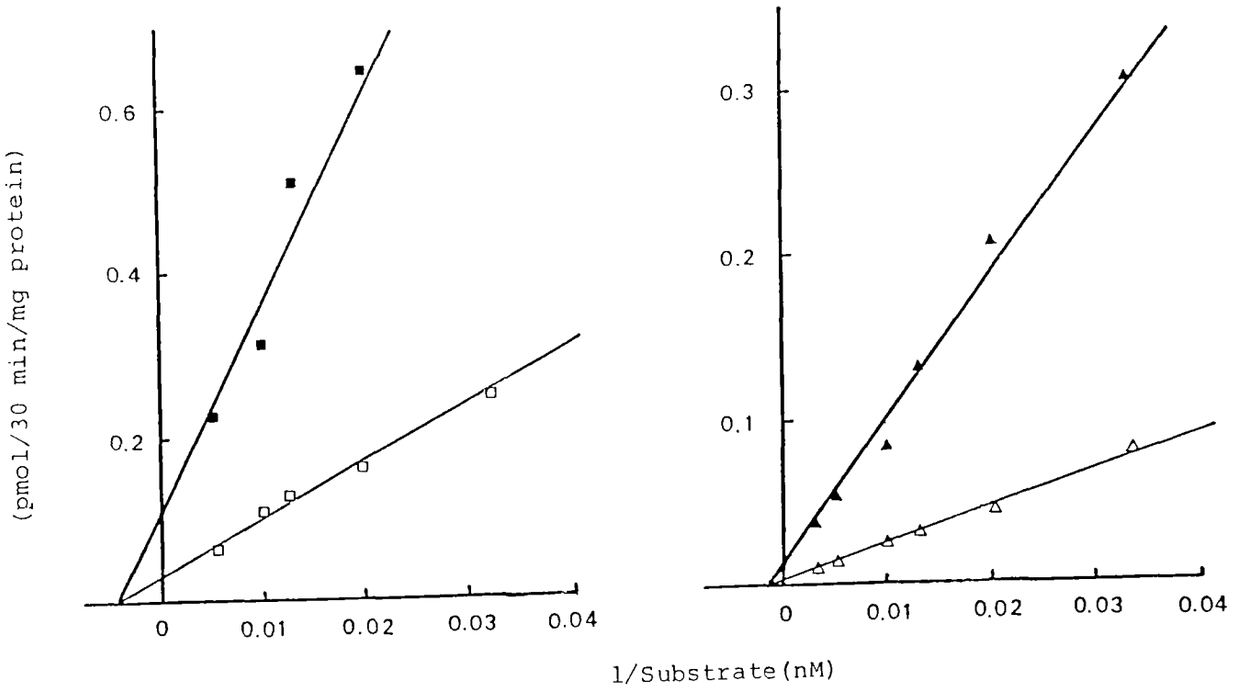

Fig. 5. Lineweaver-Burk plots of zinc inhibition of 5α-reductase(a) and 3α-hydroxysteroid oxidoreductase(b) in homogenates of rat ventral prostate with 5×10^{-4} M NADPH. Zinc absent □——□, △——△, 2×10^{-5} M zinc ■——■, 2×10^{-4} M zinc ▲——▲.

ference between two groups. The Lineweaver-Burk plot of the zinc inhibtion of 3α-HSO was as Fig 5b.

DISCUSSION

An artificial changes of intra-prostatic zinc content induce morphological and functional alteration (Lo *et al.* 1960) and an inverse relationship exists between the concentration of DHT and zinc in benign hyperplastic tissue of the prostate (Habib *et al.*, 1976). Zinc which is present in high concentration in the prostate appears to play an important role in the physiological function and testosterone metabolism of the prostate *in vivo* (Mawson and Fisher 1952).

Since Frederiksen and Wilson (1971) reported that high concentration of zinc inhibited 5α-reductase activity in the nuclear fraction of the rat ventral prostate, role of zinc in prostate has been widely investigated with a viewpoint of effect of zinc on 5α-reductase activity in the tissue of normal and benign prostatic hyperplasia. While Wallace (1975) observed continuous inhibition of enzymic activity in proportion to increment of zinc concentration, Grant *et al.* (1971), Habib (1980) and Leak *et al.* (1984a) reported dual effects of zinc. They found the enzyme activity was increased at low concentration of zinc such as 5×10^{-7} M but it was inhibited at a higher concentration than 10^{-5} M. This controversy needs to be reevaluated. Effect of zinc on enzyme activity was evaluated by estimation of accurate concentrations of the reaction medium according to the measurement of prostatic zinc contents in this experiment.

The Km value of 5α-reductase in this experiment was 0.35 μM which was similar to the Km value of 0.6 to 1 μM measured by Wilson (1975) in the nuclear fraction of the rat ventral prostate. 5α-Reductase activities were inhibited in all ranges of various concentrations of zinc throughout the whole experiment. Increased activities at lower concentrations of zinc as reported by Habib (1980) and Leake *et al.* (1984a) was not observed and, moreover, increased activities were observed when zinc content in the sample became zero by an addition of 1 mM EDTA. This result is not compatible with the hypothesis of Habib (1980) and Leake *et al.* (1984a) that production of DHT is regulated by the intibition of 5α-reductase activities at above or below the optimal concentrations.

DHT concentration is regulated not only by 5α-reductase but also by 3α-HSO, that is, it depends on the balance of intracellular activities of these two enzymes. Therefore it is desirable to analyze quantitatively the effect of zinc on both enzymes in the tissue of same animals.

There have been only very few reports about the effect of zinc on 3α-HSO activities including those of Hudson (1982) and Sinquin (1984). However, their findings are debatable. Hudson (1982) reported that the enzyme activity was not changed up to a high concentration of zinc as 2.1×10^{-3} M. The Km value of 3α-HSO in this experiment was 1.4 μM which is slightly higher than the Km value of 0.6 μM of Taurog *et al.* (1975), but the production rate of metabolites by 3α-HSO and 5α-reductase were similar between two studies. The half-inhibition concentration of zinc on 3α-HSO was 9.74×10^{-5}M which is markedly higher than 1.18×10^{-5}, that of 5α-reductase, which was almost completely inhibited at 5×10^{-4} M. The degree of inhibition of activities of both enzymes might be different because 5α-reductase is present mainly in the nuclear and microsomal fraction and 3α-HSO is present in the cytosol (Bruchovsky and Wilson, 1968; Unhjem 1970), and distribution and concentration of intracellular zinc are variable (Siegel *et al.* 1961; Dhar *et al.* 1973; Leake *et al.* 1984 b). Considering the above factors, it is very difficult to predict variations of DHT concentration quantitatively *in vivo* only by changes of total prostatic zinc concentration. However, it can be considered that concentration of DHT may be influenced by intra-prostatic zinc concentration, possibly through the balance of the two enzyme activities resulting from the difference in their sensitivities to inhibition by the metal ion.

Acknowledgemnt; We thank Prof. Young Kyoon Kim, Department of Urology, and Prof. Jung-Kyoo Lim, Department of Pharmacology, for their encouragement and discussion during the course of this work.

REFERENCES

Bertrand G, Vladesco R. Intervention probable du zinc les phenomenes defecondation chez les animaux vertebres. C.R. Seanc. Soc. Biol. Fil. 1921, 173:176-179

Bruchovsky N, Wilson JD. The conversion of testosterone to 5α-androstan-17β ol-3-one by rat prostate in vivo and in vitro. J. Biol. Chem. 1968, 243:2012-2021

Bruchovsky N, Lieskovsky G. Increased ratio of 5α-reductase: 3α(β)-hydroxysteroid dehydrogenase activities in the hyperplastic human prostate. J. Endocr. 1979, 80:289-301

Dhar NK, Goel TC, Dube PC, Chowdhury AR, Kar

AB. Distribution and concentrations of zinc in the subcellular fractions of benign hyperplastic and malignant neoplastic human prostate.Exp. Mol. Pathol. 1973, 19:139-142

Feustel A, Wennrich R, Steiniger D, Klauss P. Zinc and cadmium concentration in prostatic carcinoma of different histological grading in comparison to normal prostate tissue and adenofibromyomatosis (BPH). Urol Res. 1982, 10:301-303

Frederiksen DW, Wilson JD. Partial characterization of the nuclear reduced nicotinamide adenine dinucleotide phosphate: $\triangle^4$ -3-ketosteroid 5α-oxidoreductase of rat prostate. J. Biol. Chem. 1971, 216:2584-2593

Geller J. Albert J. Lopez D, Geller S, Niwayama G. Comparison of androgen metabolites in benign prostatic hypertrophy(BPH) and normal prostate. J. Clin. Endocr. Metab. 1976, 43:686-691

Ghanadian R, Smith CB. Metabolism of steroids in the prostate. The Endrocrinology of prostate tumours, p.113 MPS Press, Lancaster, England, 1983

Grant JK, Minguell J, Taylor P, Weiss M. A possible role of zinc in the metablism of testosterone by the prostate gland. Biochem. J. 1971, 125:21-26

Gyorkey F, Min KW, Huff TA, Gyorkey P. Zinc and magnesium in human prostate gland: normal, hyperplastic and neoplastic. Cancer Res. 1967, 27:1348-1353

Habib FK, Hammond GL, Lee IR, Dawson JB, Mason MK, Smith PH, Stitch SR. Metal-androgen interrelationships in carcinoma and hyperplasia of the human prostate. J. Endocr. 1976, 71:133-141

Habib FK. Zinc and the steroid endocrinology of the human prostate. J. Steroid Biochem. 1978, 9:403-407

Habib FK. Evaluation of androgen metabolism studies in human prostate cancer-correlation with zinc levels. Prev. Med. 1980,9:650-656

Hammond GL. Endogenous steroid levels in the human prostate from birth to old age: a comparison of normal and diseased tissue. J. Endocr. 1978, 78:7-19

Hudson RW. Studies of the cytosol 3α-hydroxysteroid dehydrogenase of human prostatic tissue: comparison of enzyme activities in hyperplastic, malignant and normal tissues. J. Steroid Biochem. 1982, 16:373-379

Leake A, Chisholm GD, Habib FK. The effect of zinc on the 5α-reduction of testosterone by the hyperplastic human prostate gland. J. Steroid Biochem. 1984a, 20:651-655

Leake A, Chisholm Gd, Busuttil A, Habib FK. Subcellular distribution of zinc in the benign and malignant human prostate: Evidence for a direct zinc androgen interaction. Acta Endocrinol. 1984b, 105:281-288

Lo MC, Hall T, Whitmore WF. Some effects of dithizone on the canine prostate. Cancer 1960, 13:401-411

Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the folin phenol reagent. J. Biol. Chem. 1951, 193:265-275

Mainwaring WIP. The mechanism of action of androgens, Springer-Verlag, New York, 1977

Mawson CA, Fischer MI. The occurrence of zinc in the human prostate gland. Can. J. Med. Sci. 1952, 30:336-339

Prout GR, Sierp M, Whitmore WF. Radioactive zinc in the prostate: Some factors influencing concentrations in dogs and men. J. Am. Med. Ass. 1959, 169:1703-1710

Prout GR, Kliman B, Daly JJ, Maclaughlin RA, Griffin PP. In vitro uptake of ^{3}H-testosterone and its conversion to dihydrotestosterone by prostatic carcinoma and other tissues. J. Urol. 1976, 116:603-610

Schrodt GR, Hall T, Whitmore WF. The concentration of zinc in diseased human prostate glands. Cancer 1964, 17:1555-1556

Siegal E, Graig FA, Drystal MM, Siegal EP. Distribution of Zn^{65} in the prostate and other organs of man. Br. J. Cancer, 1961, 15:647-664

Sinquin F, Morfin R, Charles JF, Floch HH. Testosteronemetabolism by homogenates of human prostates with benign hyperplasia: Effect of zinc, cadmium and other bivalent cations. J. Steroid Biochem. 1984, 20:773-780

Taurog JD, Moore RJ, Wilson JD. Partial characterization of the cytosol 3α-hydroxysteroid-NAD (p) + oxidoreductase of rat ventral prostate. Biochemistry 1975, 14:810-817

Unhjem O. Partial seperation of 3α-ketosteroidoxidoreductase and an androgen binding substance present in rat ventral prostate cytoplasm. Acta Endocrinol. 1970, 65:525-532

Vallee BL. The biochemistry, physiology and pharmacology of zinc. Physiol.Rev. 1959, 39:443-490

Wallace AM, Grant JK. Effects of zinc on androgen metabolism in the human hyperplastic prostate. Biochem. Soc. Trans. 1975, 3:540-542

Wilson JD. Metabolism of testicular androgens. In: Greep R.O., Astwood E.B. (eds) Handbook of Physiology, Sect. 7 vol. 5: Chap 25. American Physiological Society, Washigton DC, 1975

= 국문초록 =

흰쥐 복측전립선 Androgen 대사에 미치는 Zinc의 효과*

이종욱 · 박찬웅 · 신상구 · 송동근

서울대학교 의과대학 약리학교실

전립선내 androgen대사에 미치는 zinc의 효과를 관찰하고자 DHT 농도결정에 주 역할을 하는 5α-reductase와 3α-hydroxysteroid oxidoreductase(3α-HSO)의 활성도에 미치는 zinc의 효과를 흰쥐 복측전립선 homogenate를 사용하여 관찰하였다.

1. 흰쥐 복측전립선의 zinc 함량은 평균 29.92±5.56(S.E.) μg/mg wet weight 이었다.

2. 5α-reductase 활성도는 zinc 농도 10^{-5} M 이상에서 유의한 언제를 보였으며, 1012—123 M 농도에서는 86%의 억제를 보였다. 3α-HSO 활성도는 5×10^{-5} M 이상의 농도에서 유의한 활성도 억제를 보였으며, 10^{-3} M 농도에서는 93%의 억제를 보였다.

3. 5α-reductase의 Km 치는 testosterone 농도 353.5 nM, 최대활성도 (V_{max})는 평균 41.8 pmol/30 min/mg protein이었고 zinc에 의해서 비상경적 양상으로 억제되었고, 활성도를 50% 억제하는 zinc의 농도는 평균 1.83×10^{-5} M 이었다.

4. 3α-HSO의 km 치는 dihydrotestosterone (DHT) 농도 1477.2 nM, 최대 활성도 (V_{max})는 평균 823.2 pmol/30 min/mg protein 이었고, zinc에 의해 비상경적 양상으로 억제되었으며, 활성도를 50% 억제하는 zinc 농도는 평균 9.74×10^{-5} M 이었다.

이상의 실험결과로 타 장기에 비해 높은 함량으로 전립선내에 내재하는 zinc는 그 함량변화에 의하여 testosterone에서 DHT로의 대사전환에 관여하는 효소인 5α-reductase와 DHT에서 3α-diol로의 대사전환에 관여하는 3α-HSO의 활성도에 영향을 끼침으로써 전립선내 활성형 androgen인 DHT의 농도조절에 관여하리라 추정하였다.

* 본 연구는 1985년도 문교부 학술연구조성비의 지원으로 이루어졌음.