Structure and physiology of mammalian vas deferens in relation to fertility regulation

N. J. CHINOY

Department of Zoology, University School of Sciences, Gujarat University, Ahmedabad 380 009, India.

Abstract. The structural and functional integrity of the vas deferens and its role in ensuring the fertilizing ability, viability of spermatozoa and their survival in the vas deferens, are elucidated. The regulation of the function of the vas deferens and the differential androgen dependency of its two regions have been discussed in relation to its secretory and absorptive activities as well as its contractility. The importance of ascorbic acid in maintaining its functions has also been investigated.

The potentiality of the use of an androgen antagonist, steroids (testosterone, estradiol benzoate), prostaglandins, copper devices, vasectomy, vasocclusive agents, effects of nutritional deficiencies, human chorionic gonadotropin-antiserum and plant products as antifertility agents have been discussed.

Keywords. Vas deferens; fertility regulation.

Introduction

The progress in the development of new agents for male contraception acting specifically at vas deferens level necessitates a clear understanding of the hitherto inadequately understood basic machanisms controlling its structure and internal milieu. The present review attempts to bridge some of the lacunae and it is based on research carried out in the author's laboratory during the last 15 years.

Structure of vas deferens

Morphologically, the vas deferens can be differentiated into two regions, the proximal vas deferens which is near cauda epididymis and the distal vas deferens adjacent to the accessory gland complex. A significant difference exists in the diameter of these two regions as the distal region possesses a thicker muscular coat than the proximal.

Histologically, each region of the vas could be differentiated from the other on the basis of the characteristic epithelium, lamina propria, shape of lumen and the presence or absence of folds in the epithelium (Chinoy and Chinoy, 1982).

Studies on the ultrastructural characteristics of the two regions of rat, hamster and

---

Abbreviations used: 5α-DHT, 5α-Dihydrotestosterone; CA, cyproterone acetate; AA, ascorbic acid; ISCD, intrascrotal copper device, IECD, intraepididymal copper device; IVCD, intravasal copper device.

monkey vas deferens have been carried out (Flickinger, 1973, 1975; Flickinger *et al.,* 1978; Prakash, 1980; Prakash *et al.,* 1979; Chinoy and Asok Kumar, 1982). The pseudostratified columnar epithelial cells of the two regions could be classified into tall, thin principal cells studded with long stereocilia, small round pyramidal basal cells and osmiophilic, mitochondria-rich cells. The occurrence of different cell types varies in different mammals.

Flickinger (1973) and Hoffer (1976) suggested on the basis of structural features that the proximal vas deferens functions in the synthesis of proteins/glycoproteins and in the absorption of material from the lumen. On the other hand, the distal vas deferens synthesizes steroids by virtue of possessing abundant smooth endoplasmic reticulum. However, ultrastructural and biochemical studies on the rodent vas deferens in the author's laboratory have clearly elucidated that inspite of the existing structural differences, no rigid functional demarcation of the proximal and distal vas into absorptive and synthesizing/secretory regions could be made. It is therefore suggested that both the regions of the rodent vas deferens possesses absorptive, synthetic and secretory activities to a variable degree (Chinoy and Chinoy, 1979; Chinoy and Chinoy, 1982; Chinoy and Asok Kumar, 1982).

The histochemical localization of ascorbic acid in the vas deferens of rat, mouse, guinea pig and human beings, using a modified technique (Chinoy and Sanjeevan, 1978) revealed that the staining pattern was the same in all cases, wherein, the nuclei were stained more intensely as compared to the cytoplasm. The luminal spermatozoa were also darkly stained (Chinoy *et al.,* 1983).

A comparative study of various histophysiological features of proximal and distal vas deferens as well as epididymis in albino rats, guinea pigs and mouse elucidated that the vas deferens is not a mere conduit for sperm transport, but is an important organ contributing actively to the maintenance of sperm structure, maturation, survival and viability (Chinoy *et al.,* 1983a; Chinoy and Chinoy, 1982). It is also known that in azospermic men with bilateral blockage of corpus and cauda epididymis, successful pregnancies have been reported following epididymovasostomy (Young, 1970).

The epididymis and sex accessory glands have different threshold requirements of androgens for the maintenance of their structure and metabolic activities in various animals. Similarly, Chinoy, and Chinoy (1983a) reported that the proximal and distal vas deferens of albino rats possessed differential sensitivity to testosterone. The distal vas deferens possessed a higher threshold requirement for testosterone for the maintenance of its structural and biochemical integrity than the proximal vas deferens. Moreover, ascorbic acid had a potentiation effect on androgen action as reported earlier for the epididymis (Chinoy, 1978, 1984; Chinoy *et al.,* 1982).

Studies on the uptake and binding of testosterone in vas deferens of rat and mouse as well as rhesus monkey (Applegren, 1969; Thampan *et al.,* 1979) revealed that the major detectable androgen was 5α-dihydrotestosterone (5α-DHT). The vas showed a metabolic pattern similar to that of epididymis, but with predominant 5α-DHT receptors and having greater affinity for testosterone binding in comparison with prostate and seminal vesicle.

The normal vas deferens of rodents manifested a differential contractile response on the left and right sides in correlation with their calcium and electrolyte levels (Chinoy and Chinoy, 1983a).

Vas deferens as a site for control of fertility in male

Androgen antagonist

The effects of cyproterone acetate (CA) treatment for 7, 15, 30 and 60 days on proximal and distal vas deferens of rats and guinea pigs were studied. Androgenic parameters in distal part were more affected than in the proximal, indicating its differential androgen sensitivity. The spontaneous contractility of the vas and its adrenergic response were reduced by CA treatment. It is suggested that the antifertility effects of CA are not only due to loss of motility and fertilizability of sperms, the alterations in their morphology but also due to changes in the contractile pattern of the vas (Chinoy, 1984; Chinoy and Chinoy, 1979; Chinoy *et al.,* 1982). Combined CA + ascorbic acid (AA) treatment caused recovery in spontaneous contractions and metabolism of the two regions although the per cent motility and fertilizability of sperms were not improved. The results indicate the prophylactic action of AA following CA treatment without interference with its contraceptive effects. The antiandrogenic effects of CA were transient and reversible after the withdrawal of the treatment.

Prostaglandins

It is known that PGE1 and PGF2a are pharmacodynamically potent smooth muscle stimulants and are involved in contractility of vas deferens and sperm transport. Subcutaneous injections of 100 μg PGE1 and PGF2a per day/rat for 30 days manifested definite antiandrogenic and antifertility effects (Chinoy and Chinoy, 1981). The two prostaglandins altered the histology, metabolism and adrenergic response of the vas deferens in comparison to the control. The sperm density and motility were significantly affected and they revealed acrosomal, midpiece and tail damage.

Comparison of the effects of the two PGs showed that PGF2a was more effective in altering contractile pattern and Cholinesterase activity of the vas, whereas, its metabolism, sperm morphology and density were affected more by PGE1. However, both PGs caused 50 % reduction in fertility rate and almost the same level of reduction in sperm motility and protein levels. Thus both PGs have partial antifertility effects as they alter the sperm morphology and antagonize the adrenergic response of the vas deferens by blocking the α-adrenoreceptors.

Copper wire implants

A comparative study on the effects of copper wire device implantation at three sites, *viz.,* intrascrotal copper device (ISCD), intraepididymal copper device (IECD) and intravasal copper device (IVCD) was carried out in albino rats (Chinoy and Sanjeevan, 1980; Chinoy and Chinoy, 1983b). All the three treatments resulted in reduced sperm count, motility, alterations in sperm morphology which in turn caused reduction in fertility of the rats especially by IECD treatment. Besides the spermicidal effect of copper ions, the alterations in histophysiology of the vas deferens also contributed in affecting its metabolism. Although, on the whole, IVCD and IECD were more effective, they were less practical as the method of implantation of the device is not simple and its

removal involves another surgical procedure, whereas, ISCD being a comparatively simpler technique, needs further attention. The antifertility effects of IVCD in rats and monkeys has also been investigated by others (Ahsan *et al.,* 1976; Khatoon, 1978).

Vasocclusion

Vasocclusion was induced by a single injection of ethanol, prostaglandin or ascorbic acid into the vas deferens (Sharma *et al.,* 1983; Chinoy and Chinoy, 1984). The sluggishly motile or comparatively immotile, abnormal and decapitated sperms reduced the fertility of the animals after all the three treatments. The reduction in androgen dependent parameters was more severe in the distal vas deferens, but tissue weights were unaltered or even increased due to the presence of the sperm granuloma in the vasal lumen. The antiandrogenic effects of vas occlusion could be reversed by simultaneous ascorbic acid feeding.

Vasocclusion is a simple nonsurgical procedure which could effectively bring about antifertility effects. Therefore, by employing some more suitable occluding agents with minimum side effects, this technique could be made more efficacious.

Vasectomy

Vasectomy (30, 60, 90 days) in mature male albino rats altered sperm morphology, density and motility as well as androgenic metabolism and the histology of both the proximal and distal vas deferens accompanied by changes in the metal ion profile (Chinoy and Chinoy, 1984a). A sperm granuloma was seen in the proximal vas deferens. The ascorbate turnover was significantly altered. It is suggested that the above changes might affect the internal milieu of vas deferens. Ascorbate feeding on the other hand, brought about recovery in the histophysiology of vas deferens and thereby manifested a beneficial effect. The use of ascorbic acid in the prophylaxis of vasectomized men is suggested. In other studies (Chinoy and Sheth, 1977; Chinoy and Seethalakshmi, 1978; Chinoy *et al.,* 1978, 1982; Chinoy, 1978, 1984), the beneficial effects of AA have been elucidated in vasectomized rats.

In another study (Chinoy *et al.,* 1983b), the effects of vasectomy (6–36 months) on androgenic parameters, serum testosterone levels, metal ion and electrolyte contents were analysed and compared with azoo-, oligo-, and normospermic semen of proven fertility of closely matched age groups. The results showed that vasectomy did not cause any adverse changes in the biochemical profile of the semen, circulating levels of testosterone and in the manganese free radical spectra. However, the levels of Mn^{2+} and Cu^{2+} were lowered after vasectomy in comparison with that of normospermic men.

In recent years the sharp increase in vasectomies has been accompanied by an increase in number of vasovasostomies. The successful reversibility of surgical reanastomosis varies considerably, depending on several factors, one of the major being production of antisperm-antibodies. The high antibody titres may interfere with fertility, but whether these antibody levels drop after successful reanastomosis, remains to be investigated in detail, together with better techniques for vasovasostomy.

Estradiol benzoate treatment to intact rats

The effects of estradiol benzoate (50 μg/day/rat for 15 days) to intact male albino rats were investigated. The treatment caused significant reduction in androgen dependent parameters and the histology of androgen target tissues. This led to alterations in the milieu of epididymis and vas deferens rendering them hostile for sperm maturation, metabolism and survival, as is evident by reduced sperm motility, alterations in their morphology, which resulted in loss of fertility. The reduction in sperm counts are correlated with decrease in weight, atrophy of testis and arrest of spermatogenesis. It is evident that estradiol treatment to adult, intact male rats manifested antiandrogenic and antifertility effects (Chinoy *et al.,* 1984) mainly by directly affecting the structural and functional integrity of testis in support of our earlier data (Chinoy and Rao, 1982; Rao and Chinoy, 1983; 1984). Studies on induction of functional sterility after treatment are called for.

Similarly, human chorionic gonodotropin antiserum treatment to rats also manifested same effects as above (Chinoy *et al.,* 1982a).

Plant products as antifertility agents

Carica papaya seed extract: The physiology of vas deferens after administration of papaya seed extract, extract + AA feeding, discontinuation of the treatment for 1–2$\frac{1}{2}$ months were investigated. The results revealed that the treatment altered the physiology of vas deferns and its contractile response to different adrenalin doses in comparison to control. However, significant recovery occurred by withdrawal of treatment in all the parameters studied (Chinoy and Geetha Ranga, 1984; Verma *et al.,* 1984). Ascorbic acid feeding was effective in restoring the effects caused by androgen deficiency in the vas deferens after treatment. On the whole, the distal vas deferens was affected more by the seed extract treatment than proximal vas and recovery was slower probably due to its higher threshold requirement for androgen.

Vinca rosea leaf extract: Similar results have been obtained for the vas deferens by the administration of aqueous extracts of *Vinca rosea* leaf in albino rats (Chinoy and Geetha Ranga, 1981), as those for *Carica papaya* treatment. However, testosterone levels showed a rebound phenomenon after the withdrawal of the treatment. Further studies are needed in this direction.

Nutritional deficiency of vitamin C

Vitamin C dietary deficiency in guinea pigs markedly affected the androgen-sensitive parameters of reproductive organs. This in turn affected their internal milieu and caused changes in their metal ion profile and in the morphology, motility and density of spermatozoa in the epididymis and vas deferens. The sensitivity of vas deferens to adrenaline was also reduced in scorbutic guinea pigs which decreased their fertility rate. The primary action seems to be at the testis level and the androgen deprivation as well as partial antifertility effects are probably secondary manifestations as a consequence of the primary effects. The study elucidated that ascorbic acid is essential for maintaining the physiological integrity of the androgen target reproductive organs including vas deferens in guinea pigs (Chinoy *et al.,* 1984: Chinoy *et al.,* 1983).

Testosterone treatment

Three different doses of testosterone (1, 10, 100 *μg)* were administered to intact male rats for 5,10 and 30 days and a comparative study was carried out. The data suggests that testosterone treatment affected the histophysiology of all reproductive organs leading to infertility (Chinoy, 1984). The antifertility effects of testosterone were reported to be transient and reversible in animals and human beings (Reddy and Rao, 1972; Reddy and Prasad, 1973; Cervantes *et al.,* 1978; Melo and Coutinho, 1978; Swerdloff *et al.,* 1979).

Acknowledgements

References

Ahsan, R. K., Farooq, A., Kapoor, M. M. and Laumas, K. R. (1976) *J. Reprod. Fertil.,* **48,** 271.
Applegren, L. E. (1969) *Acta Endocrinol.,* **62,** 505.
Cervantes, A., Campos, J., de los Monteros, S. E. (1978) *Int, J. Androl. Suppl.,* **1,** 36.
Chinoy, M. R. and Chinoy, N. J. (1979) *Indian J. Exp. Biol.,* **17,** 1176.
Chinoy, M. R. and Chinoy, N. J. (1983) *Indian J. Exp. Biol.,* **21,** 335.
Chinoy, M. R. and Chinoy, N. J. (1984) *Endocrinol. Exp.,* **18,** 65.
Chinoy, M. R. and Chinoy, N. J. (1984a) *Monit. Zool Ital.,* **18,** 89.
Chinoy, M. R., Sharma, J. D., Sanjeevan, A. G. and Chinoy, N. J. (1983) *Proc. Indian Nat. Sci. Acad.,* **B49,** 628.
Chinoy, M. R., Sharma, J. D. and Chinoy, N. J. (1984) *Int. J. Fertil.,* **29,** 98.
Chinoy, N. J. (1978) *J. Anim. Morphol Physiol., Silver Jubilee Vol.,* 68.
Chinoy, N. J. (1984) *Indian Rev. Life Sci.,* **4,** 37.
Chinoy, N. J. and Asok Kumar R. (1982) *VIth Cell Biology Conf.,* Delhi, Dec. 25–27.
Chinoy, N. J. and Chinoy, M. R. (1981) *Int. J. Fertil.,* **26,** 1.
Chinoy, N. J. and Chinoy, M. R. (1982) *J. Reprod. Biol. Comp. Endocrinol.,* **2,** 1.
Chinoy, N. J. and Chinoy, M. R. (1983a) *J. Biosci.* **5,** 173.
Chinoy, N. J. and Chinoy, M. R., (1983b) *Life Sci. Adv.,* **2,** 1.
Chinoy, N. J. and Geetha Ranga M. (1981) *Proc. 2nd All India Symp. Exptl Zool.,* Baroda, Jan, 29-31st. Abst. 130, p. 77.
Chinoy, N. J. and Geetha Ranga M. (1984) *Acta Europaea Fertilitatis,* **15,** 59.
Chinoy, N. J. and Rao, M. V. (1982) *Endokrinologie,* **80,** 287.
Chinoy, N. J. and Sanjeevan, A. G. (1978) *Histochemistry,* **56,** 275.
Chinoy, N. J. and Sanjeevan, A. G. (1980) *Int. J. Androl.,* **3,** 719.
Chinoy, N. J. and Seethalakshmi, L. (1978) *Indian J. Exp. Biol.,* **16,** 1318.
Chinoy, N. J. and Sheth, K. M. (1977) *Indian J. Exp. Biol.,* **15,** 821.
Chinoy, N. J., Seethalakshmi, L. and Singh, Y. D. (1978) *Indian J. Exp. Biol.,* **16,** 162.
Chinoy, N. J., Sheth, K. M, Seethalakshmi, L., Parmar, P. Y., Sanjeevan, A. G., Rao, M. V., Sharma, J. D., Chinoy, M. R., Maithili, R. S., Trivedi, D. G., Asok, Kumar R. and Geetha Ranga, M. (1982) *Comp. Physiol. Ecol.,* **7,** 325.

Chinoy, N. J., Rao, M. V. and Seethalakshmi, L. (1982a) *Arch. Androl.,* **8,** 283.

Chinoy, N. J., Sharma, J. D. and Chinoy, M. R. (1983) *Z. Mikrosk. Anat. Forsch.,* **97,** 961.

Chinoy, N. J., Chinoy, M. R. and Sharma, J. D. (1983a) *Bull. Pure Appl. Sci.,* **2A,** 1.

Chinoy, N. J., Rao, M. V. and Seethalakshmi, L. (1983b) *Indian J. Exp. Biol.,* **21,** 193.

Chinoy, N. J., Buch, R. P.-nee- Mehta, R. R., Seethalakshmi, L., Sharma, J. D. and Chinoy, M. R. (1984) *Int. J. Fertil.,* (in press).

Flickinger, C. J. (1973) *Anat. Rec.,* **176,** 205.

Flickinger, C. J. (1975) *Biol. Reprod.,* **13,** 50.

Flickinger, C. J., Howards, S. S. and English, H. F. (1978) *Am. J. Ant.,* **152,** 557.

Hoffer, A. P. (1976) *Biol. Reprod.,* **14,** 425.

Khatoon, R. A. (1978) *Studies on non-occlusive intravasal copper device for control of male fertility,* Ph.D. Thesis, All India Institute of Medical Sciences, New Delhi, India.

Melo, J. F. and Coutinho, E. M. (1978) *Int. J. Androl. Suppl.* **1,** 138.

Prakash, A., (1980) *Light and electron microscopic studies on the excurrent ducts of the male reproductive system in the adult rhesus monkey,* Ph.D. Thesis, Delhi University, Delhi.

Prakash, A., Prasad, M. R. N. and Anand Kumar, T. C. (1979) *J. Biosci.,* **1,** 185.

Rao, M. V. and Chinoy, N. J. (1983) *Europ. J. Obstet. Gynecol. Reprod. Biol.,* **15,** 189.

Rao, M. V. and Chinoy, N. J. (1984) *Exp. Clin. Endocrinol.,* **84,** 211.

Reddy, P. R. K. and Rao, J. M. (1972) *Contraception,* **5,** 295.

Reddy, P, R. K. and Prasad, M. R. N. (1973) *Contraception,* **7,** 105.

Sharma, J. D., Chinoy, N. J. and Dixit, V. P. (1983) *Exp. Clin. Endocrinol,* **82,** 337.

Swerdloff, R. S., Arthur-Camfield, L., Palacicos, A., and McClure, R. D. (1979) *J. Steroid Biochem.,* **11,** 663.

Thampan, T. N. R. V., Dinakar, N., and Prasad, M. R. N. (1979) *Indian J. Exp. Biol.,* **17,** 290.

Verma. R. J., Sam, M. G. and Chinoy, N. J. (1984) *Proc. 4th Ann. Symp. Reprod. Biol. Comp. Endocrinol.,* PGIBMS, Madras 7–8 June.

Young, D. (1970) *J. Reprod. Fertil.,* **23,** 541.