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Prostate Gland: Structure, Functions and Regulation

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The prostate gland plays an important role in male reproduction. It secretes enzymes, lipids, amines and metal ions essential for the normal function of spermatozoa. Development, differentiation and maintenance of the prostate gland depend on steroid and peptide hormones. Beside hormones growth factors also regulate the prostate gland. This review will focus on the structure, functions and mode of regulation of the prostate gland.

Introduction

The prostate, the largest male accessory gland, surrounds the urethra at the neck of the urinary bladder. In an axial view the gland appears round, elliptical or triangular in shape. It weighs only a few grams at birth and approximates 20 g by the age of 20 years. Thereafter its weight and histology are stable for another 25 years.

Structure. It is encapsulated by a thin fibroelastic tissue layer which gives it an unlobulated appearance. However, the fibroelastic capsule gives rise to septa which extend inward and subdivide the prostate into five lobes: an anterior, a posterior, a medial and two laterals [1]. These lobes lodge 30–50 branched tubuloalveolar or saccular glands, 16–32 excretory ducts, dense stroma, blood vessels, lymphatics and nerves [2]. Although the normal prostate cannot be divided into lobes, there is a tendency towards lobulation as benign prostatic hyperplasia progresses [1].

Histologically, the prostate is divided into two major zones: a central and a peripheral. The two zones have distinct features, as shown in Table 1 [3]. In addition a transitional zone, an anterior segment and a preprostatic sphincteric zone have also been identified [4].

The normal human prostate gland of the young adult has five types of acinar cells [5].

1. Microvillar cells have numerous microvilli on the apical surface.
2. Secretory cells show active secretion and bulging of the apical cell membrane.
3. Holey cells possess one to several small holes on the apical cell surface.

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Table 1
Features of central and peripheral zones of the prostate

Feature	Central zone	Peripheral zone
Branching of duct system	Elaborate	Simple
Size of terminal sacculations	Large	Small
Stroma	Dense, collagen rich	Loose, delicate
Acini arrangement	Lobular	Evenly distributed

4. Crater cells have broken apical cell membrane.

5. Bare cells have fairly smooth apical surface with scant microvilli at the periphery.

Besides these cell types basal cells, stem cells and neuroendocrine cells are also found in the prostate [1].

Prostatic secretion is a homogeneous, serous and slightly acidic (pH 6.6) milky fluid with low (<1%) protein content. It constitutes nearly 0.5 ml of average 3–3.5 ml of the normal human ejaculate. The constituents of prostatic secretion include various enzymes, lipids, metal ions and amines, as shown in Table 2.

Table 2
Constituents of prostatic secretion

Acid phosphatase	Fibrinolytic enzymes
Albumin	Inositol
a-Amylase	Magnesium, zinc, sodium
β-Glucuronidase	Plasminogen activator
Cephalin	Phospholipids
Cholesterol	Seminin
Choline	Proteolytic enzymes
Citric acid	Spermine
Dermatan	Spermidine
Diastase	

Embryology and development. The prostate makes its appearance at the 11th week of gestation as multiple solid outgrowths of the urethral epithelium both above and below the entrance of mesonephric duct. The epithelial buds branch and rebranch to form the complex ductal system of the prostate. Five distinct groups of epithelial buds are formed which develop into five internal lobes of the prostate. The anterior lobar tubules shrink, lose their branches, lumen and appear as small, solid embryonic epithelial outgrowths at birth. The mesenchymal cells which are present around the ductal systems, become denser at the periphery and form the prostatic capsule. By the 22nd week, a muscular stroma is considerably developed which continues to progressively

increase until birth [6]. Postnatal development of the human prostate proceeds in the following phases: (i) a regression period after birth; (ii) a quiescent period up to 12–14 years and (iii) a maturation period between 14 and 18 years. No lobe formation is observed during postnatal development [7].

Functions

The prostate gland has various useful functions:

1. Physically, through its mass and musculature, it participates in the control of urine output from the bladder and in the transmission of seminal fluid during ejaculation [8].
2. As an exocrine gland, it contributes to the seminal plasma a spectrum of small molecules and enzymes like fibrinolysin, coagulase and other coagulum lysing enzymes which facilitate fertility and are involved in coagulation [1].
3. Prostatic fluid safeguards sperm viability by reducing the acidity of the urethra. It facilitates and enhances sperm motility by contributing a certain factor (albumin) to seminal plasma that stimulates the motility of epididymal and washed ejaculated spermatozoa [1].
4. Prostatic acid phosphatase, by hydrolysing phosphorylcholine to choline is directly involved in the nutrition of spermatozoa [1].
5. As an endocrine gland, it helps rapid metabolism of testosterone to more potent androgen dihydrotestosterone (DHT) and thus also influences both hypothalamic and hypophyseal functions [8].
6. The high level of zinc in human seminal plasma appears to originate primarily from the secretion of prostate gland which acts as an antibacterial agent [9].

Regulation by hormones

The majority of our current understanding of the regulation of prostate has been derived from studies carried out on rat ventral prostate.

Morphology and ultrastructure

Steroid hormones: The prostate is one of the target organs for the action of androgens. Besides androgens other steroids like oestrogen and progesterone also regulate the growth of the prostate [10].

Androgens: The dependence of the prostate gland on the presence of testicular hormones for maintenance of its structural and functional integrity is well known [11, 12]. Withdrawal of this hormonal support, as by orchiectomy, results in drastic metabolic changes and an accelerated rate of tissue involution in the prostate – a process known as autophagia [13]. At the subcellular level, testosterone or androstenedione maintain the prostatic epithelium, preserve microvilli, the Golgi apparatus and the endoplasmic reticulum [14]. The ventral prostate of

the rat when cultured without androgens shows a marked involution of the components of the Golgi apparatus, disappearance of secretory granules, microvilli and regression of the rough endoplasmic reticulum [14]. Ribosomes also decrease in number and tend to become isolated instead of being associated in polyribosomes. Nuclei shrink and become irregular with deep invaginations. Nuclei decrease in size and the perichromatin granules are reduced in number. Immunization with testosterone too leads to reduction of weight of the prostate [15].

Testosterone and its principal metabolite, DHT, can suppress stromal growth and foster increase in epithelial height and secretory activity. DHT, being five times more potent than testosterone, evokes extensive hyperplasia at higher doses. Adrenal steroids have also been implicated in maintaining the prostate gland [16].

Oestrogens cause a regression of the sex accessory glands in male rats [17]. However, the ultrastructure of the prostate from oestrogen-treated males is generally indistinguishable from castrates [18]. Oestradiol is believed to affect the prostate both directly at cellular level and indirectly via gonadotropin inhibition at the level of the hypothalamus or pituitary gland [19]. Oestradiol exerts its antiandrogenic effect on the epithelium of intact animals resulting in lower epithelial height and reduction in the number of cell organelles and secretory bodies and has no discernible effect upon the glandular epithelium in castrates. Testosterone alone can restore glandular morphology to normal in these animals. Oestrogen in combination with testosterone can prevent regeneration of the rough endoplasmic reticulum and elicits the formation of large lipid like inclusions and the accumulation of secretory bodies in the apical zone of many cells [20]. Brief administration of oestrogen to newborn rats results in permanent suppression of prostate growth and reduces prostatic responsiveness to testosterone in adulthood [21].

In castrates, the prostatic stroma becomes thickened with a large increase in fibrous material between and surrounding each acinus, although smooth muscle cells retain their normal cytology. In response to oestradiol treatment, alone or in combination with testosterone, smooth muscle cells increase in size and number. The organelles decrease in number, the cytoplasm becomes more electron dense and the nuclei turn more heterochromatic. Surface vesicles are profuse in smooth muscle cells in animals treated with oestradiol alone. Large phagocytic vacuoles are characteristic of the glands of animals treated with oestrogen and testosterone in combination [20].

Gestagens: Besides testosterone and oestrogens, progesterone also regulates the prostate gland by virtue of its androgenic activity. When given to castrated male rats progesterone and progestins maintain or stimulate the weight, cytology and secretory functions of the prostate [22].

Peptide hormones

Prolactin, a hypophyseal hormone, has synergistic action on androgen induced weight gain and citric acid secretion by the lateral prostate of the rat,

and also has a direct effect on the growth of the latter [23]. It increases prostatic accumulation of both testosterone and DHT [24], while antiprolactin, bromocriptine suppress the uptake of testosterone [25]. Hypophysectomy causes a more profound atrophy of the rat prostate than does castration. Immunization with prolactin and injection of prolactin antiserum inhibit prostate growth [26].

Insulin, a peptide hormone regulating blood glucose, is also required for normal growth of the prostate. Severe diabetes results in castrate-type accessory organs [27]. Insulin treatment of diabetic rats is necessary to obtain prostatic response to testosterone [28]. In diabetic animals the prostatic epithelium shows a lower cell height, a diminution in secretory granules and the presence of autophagic vacuoles [28].

Proteins and nucleic acid synthesis

The net tissue contents of DNA, protein and mRNA coding for these proteins decrease after castration and are restored to normal by replacement of androgen [29–33]. The enhancement of DNA synthesis by androgens is organ specific and both nuclear and mitochondrial DNA syntheses increase [34]. Similarly, the transcription machinery is also switched on which is evident by increased rRNA synthesis, nucleolar RNA polymerase activity and polyribosome formation [35, 36]. The protein content of the prostate decreases during castration as a result of a combined effect of an accelerated rate of protein degradation and a reduced rate of protein synthesis. On the other hand, several intracellular proteins whose functions are unknown increase in the prostate after castration [37]. The effect of androgen supplementation is preceded by an increase in nuclear RNA synthesis [38, 39]. The androgenic effects appear to be directed towards unwinding of DNA or movement of the enzyme along the template [40]. Androgens also regulate the translational machinery. The effect of androgens on the activity of protein initiation factors occurs immediately after it enters the target cell [41]. The ^{35}S-Met-tRNA$_f$Met binding to prostate ribosomes is enhanced within 10 minutes of androgen injection in castrated rats [42, 43]. Androgens induce aldolase mRNA and the synthesis of poly (A)-enriched 6–15 S mRNA fraction in a highly tissue and steroid specific manner [44, 45]. Androgens also regulate the transcriptional capacity of the C_1, C_2 and C_3 prostatic binding protein genes and are known to play a major role in determining mRNA stability in the rat ventral prostate [46]. The expression of mRNA for dorsal protein 1 is androgen dependent [47]. Prolactin is known to synergize the action of androgens. Simultaneous injection of DHT and prolactin to mature castrated rats augments the level of DNA, RNA and proteins to normal levels [48, 49]. Likewise, prolactin injection to intact mature male rats significantly increases both DNA and RNA in the ventral prostate gland [48]. A direct, auxiliary action on prostatic protein synthesis has also been reported for insulin [50, 51].

Enzyme activities

The stimulation of prostatic DNA-dependent RNA polymerase by androgens has been well documented [31, 52, 53]. Both nucleolar and extra-nucleolar RNA polymerase activities can be stimulated by androgens [54]. The association of steroid-receptor complexes with chromatin causes enhanced template activity resulting in increased transcription by exogenous and endogenous RNA polymerase B [55]. The stimulation of RNA polymerase activity by DHT is effectively inhibited by diethylstilboesterol [52, 56].

DNA polymerase and DNA lipase activities are remarkably enhanced by androgenic stimulation [57]. Nicking closing enzyme activity decreases after castration. However, its activity can be maintained or returned to normal values by the administration of DHT [58]. DNA unwinding activity and prostatic thymidine kinase activity are also regulated by androgens in a highly steroid and tissue specific manner [57].

Testosterone by producing an inhibitory modulator of phosphodiesterase brings down the levels of cAMP and phosphodiesterase to normal in castrated rats. This regulation of cAMP considerably influences several prostatic enzymes that are involved in carbohydrate metabolism [59, 60].

The activities of L-ornithine decarboxylase and S-adenosyl-L-methionine decarboxylase are dramatically enhanced in the ventral prostate of castrated rats in response to androgenic stimulation [61, 62]. Orchiectomy results in significant decline in methylthioadenosine phosphorylase and chromatin associated protein phosphokinase activities in the rat ventral prostate which is reversed by testosterone treatment [63]. The decrease in activities appears to precede measurable changes in the protein and RNA contents [64].

Steroid receptor

All of the steroids mediate their biological effects through an interaction with steroid-specific intracellular receptors. Receptors for androgen (AR) [65], oestrogen (ER) [66], progesterone (PR) [67] and glucocorticoids (GR) [68] have been demonstrated in the human prostate. Regulation of these receptor sites by hormones is well established and has been studied in rat models [69–72]. Prostatic AR gradually increases during the early postnatal period to a peak around the time when the rat attains sexual maturity [73]. Upon ageing there is a diminution in the androgen binding sites [74, 75]. Treatment with exogenous testosterone increases AR content in aged rats to values identical to those of young mature rat prostates [75]. The concentration of AR in the cytoplasm of the prostatic cell undergoes a rapid increase within 24 hours after castration [76]. This is matched by a concomitant decrease in the concentration of free androgen in the nucleus and in the nuclear receptor [77]. However, the net concentration of receptor in a cell remains constant [77, 78]. The nuclear receptor is replenished within minutes after a single intravenous injection of androgens to castrated rats [75, 77, 79]. If the period of androgen withdrawal

in these castrated animals extends to 4–7 days, there is a progressive decline in the pool of cytoplasmic receptors which could be due to an increased proteolytic activity in the prostate [77, 80–82]. Although the level of AR declines after castration, the level of mRNA for AR is high [83]. Oestrogens also increase cytosolic and nuclear AR content of the prostate in castrated dogs either alone or in synergism with androgens [84–86]. A similar effect is also observed in normal as well as experimental prostatic carcinoma of rats [70, 87]. Oestrogen-dependent positive regulation of AR has been reported for both human and canine prostates [71, 88]. Oestrogens have also been shown to induce the PR content of dog prostate [71]. The oestrogen-mediated upregulation of AR content has been postulated to be mediated via the ERs [70]. ER, although present in the prostate of intact male rats, are undetected after 3 days postcastration and the levels recover 15 days after castration [89]. This matches with a rise in mRNA for ER over normal levels [90].

Steroid hormones have also been reported to elicit their effect through regulation of growth factors, their receptors or both in their respective target tissues.

Regulation by growth factors and growth suppressors

Growth factors along with a number of growth modulators present within the prostate gland are involved in intracellular signalling. There is a balance between factors that activate and factors that suppress growth. The inhibitory elements are called suppressors. Both stromal and epithelial cells of the prostate themselves can synthesize and respond to growth factors in a reciprocal and interactive manner. Many of these growth factors appear to be under hormonal regulation particularly in response to androgens, oestrogens and other endocrine factors. Androgens and growth factors can also stimulate the synthesis and degradation of extracellular matrix components that can alter cellular responses to steroids and growth factors [91, 92]. Growth factors can work internally in the cell (intracrine) or can be secreted extracellularly to serve as signals to its own cell in which it was synthesized (autocrine) or stimulate a nearby cell (paracrine) [1]. After being secreted the growth factors bind to specific growth factor receptors that reside on the plasma membrane of the target cell. This in turn activates a series of second messenger signals that involve protein kinases, membrane phospholipases or G protein pathways [92].

Growth factors reported to be present in the prostate include fibroblast growth factor (FGF), epidermal growth factor (EGF), transforming growth factor-beta (TGF-β), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF) and nerve growth factor (NGF).

FGF is of two types, basic and acidic [93]. It is the basic FGF (bFGF) which plays an important role in the prostate and is a broad-spectrum mitogen that can stimulate angiogenesis [93]. EGF and its receptor (EGF-R) have been localized in the prostate [94] and the EGF-R can be regulated by androgens [95]. TGF-a, a structural analogue of EGF, has been shown to stimulate the

growth of cancer cells of the human prostate in culture and to produce epithelial hyperplasia in the prostatic lobe of male mice [96].

TGF-β has two genes: TGF-β 1 and TGF-β 2. Both of these factors are present in the prostate [97]. TGF-β has a negative regulatory effect on epithelial cell growth while it is a positive factor for stromal growth [97, 98]. In addition, TGF-β is also an angiogenetic factor and can regulate neovascularization [1]. Two other factors related to TGF-β are Mullerian inhibitory substance and inhibin. The synthesis of inhibin in the prostate is regulated by hormones [99, 100].

IGFs (somatomedin) occur in two closely related forms, type I and type II, and are single chain polypeptides that share sequence homology with proinsulin. Insulin-like substances have also been detected in the prostate [101]. PDGF, a strong mitogen, has also been shown to be expressed in prostatic tumour models and cells in culture [102, 103].

NGF-like protein is localized predominantly to the stromal components of normal, benign prostatic hyperplasia and adenocarcinomatous prostate; while NGF-R is localized predominantly to the epithelial cells of the prostate thereby mediating paracrine interactive growth modulation of the human prostate [104].

The combination of steroid hormones and different growth factors and their sequence of action on different cells of the prostate at various stages of development are quite complex. Their exact mechanism of action still remains an important area in understanding the biology and pathology of the prostate.

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