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INFLAMMATION, HORMONE IMBALANCE: A PREDISPOSING FACTORS OF BENIGN PROSTATIC HYPERPLASIA: GENERAL REVIEW

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ABSTRACT

Benign prostatic hyperplasia (BPH) continues to be a significant healthcare problem world-wide. Recently published data suggest that clinical BPH, which is hallmarked by the occurrence of moderate-to-severe lower urinary tract symptoms (LUTS), occurs in about one quarter of men in their 50s, one third of men in their 60s, and about half of all men 80 years or older. Inflammation of the prostate may represent a mechanism for hyperplastic changes to occur in the prostate. There are a variety of growth factors and cytokines that may lead to a proinflammatory process within the prostate. In fact prostatic inflammation may represent an important factor in influencing prostatic growth and progression of symptoms. Prostatitis, a histological diagnosis, has evolved over the years to describe a clinical syndrome that was believed to be associated with prostatic inflammation. In addition, the altered endocrine status of aging men is likely to be of importance for development of the disease since testosterone and growth hormone (GH) levels decrease with age, whereas estrogen levels increase. Conflicting data exist on changes in prolactin hormone (PRL) levels with increasing age. As the number of men afflicted by these diseases will only continue to grow with the aging population, further understanding of the role of inflammation in BPH and hormone imbalance will expand our understanding of BPH pathogenesis, its histological and clinical progression.

KEYWORDS: Benign prostatic hyperplasia, Prostatic cytokines, Inflammation, Prostatitis, Hormone imbalance.

INTRODUCTION

Prostate disease in the form of both benign hyperplasia and malignancy is an increasingly common clinical problem in the aging male population. Although efforts to gain insight into the etiology of these conditions have increased during the past decade, a detailed understanding of the pathophysiological processes involved is still lacking.[1] Pathologic BPH is the histological determination of non-neoplastic new prostatic growth in adult men. Autopsy studies have revealed that the prevalence of pathologic BPH increases markedly after the 4th decade and is found in up to 90% of men over age 80.[2] The high prevalence of BPH in older men has led some to consider prostatic hyperplasia to be a ubiquitous result of aging.[3] Prostatic inflammation could be a key component in prostate enlargement and BPH progression. Prostate research has traditionally focused on the action of androgens in the gland.[1] The purpose of this review is to describe the prostatic inflammation and hormone imbalance that leading to prostatic diseases, such as benign prostatic hyperplasia.

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Prostate gland

The human prostate is an androgen regulated exocrine gland surrounding the urethra just below the urinary bladder, in front of the rectum. The mature walnut-sized gland consists of branched alveolar-ductal structures embedded in a fibromuscular stroma.[4] The mean weight of the normal prostate in adult males is about 11 grams, usually ranging between 7 and 16 grams. There are three anatomical prostatic glandular zones: the peripheral (PZ), the transitional (TZ),and the central zone (CZ).The

secretory epithelium is mainly pseudostratified, comprising tall columnar cells.[5] The prostate epithelium also composes of basal epithelial cells, which are supported by a fibro-elastic stroma containing randomly oriented smooth muscle bundles, Neuroendocrine cells, non-epithelial fixed macrophages and intra-acinar lymphocytes.[6] The epithelium is physically separated from the stroma by a basement membrane.[7] Under normal physiological conditions, prostatic epithelial cells are stimulated by androgens to undergo proliferation and differentiation. Cells with accumulated damage are removed by apoptosis and a steady state balance is maintained between cell proliferation and apoptosis. However certain pathological assaults may trigger the hyper stimulation of androgen and/or growth factors, thus affecting the delicate balance of prostatic cell growth and death. Consequently, a subset of epithelial cells may evade the normal checkpoint control of cell cycle progression and proliferate aberrantly.[6]

The prostate is a key gland in the sexual physiology of male mammals. It influences several vital functions related to maturation and ejaculation. Androgenic hormones are known to control differentiation of the prostate gland during male embryogenesis and its subsequent growth throughout the lifespan.[8] Accumulation and secretion of extraordinarily high levels of citrate is one of the principal functions of the prostate gland of humans and other animals. It also secretes a slightly alkaline fluid, milky or white in appearance, which in humans usually constitutes roughly 30% of the volume of the semen, which is rich in enzymes, amines, lipids and metal ions, essential for the normal function of the spermatozoa.[9] While secretion of zinc thought to stabilize the sperm chromatin, and acid phosphatase.[10] Functionally, the prostate reaches maturity at puberty. After achieving adult size, the prostate remains essentially the same size for several decades. Then, in midlife and beyond, prostatic growth occurs again in majority of the men. The explanation for this reawakening of the prostatic cells is still unclear.[4]

Factors stimulate prostate growth

factors recognized to stimulate prostate growth are insulin-like growth factors (IGFs) I and II, several epidermal growth factors (EGFs), and transforming growth factor a (TGF-a).[11] On the other hand, a few inhibitory growth factors have been discovered, whose prototype is transforming growth factor b (TGF-b), the first identified member of a super-family of growth factors including >25 proteins. TGF-b is a ubiquitous multifunctional polypeptide, acting through an androgen-independent pathway, which regulates epithelial cell proliferation and differentiation, apoptosis, extracellular matrix formation, and degradation.[12]

Benign prostatic hyperplasia (BPH)

BPH is correctly defined as enlargement of the prostate gland from the progressive hyperplasia of stromal and glandular prostatic cells.[2] It is one of the most common abnormalities of the prostate. The disease is characterized by an increase in the cell count leading to overgrowth of two types of cells, epithelial and stromal cells,[13] resulting in the formation of large, fairly discrete nodules in the transition zone of the prostate.[14] When it is sufficiently large, the nodules impinge on the urethra and increase resistance to flow of urine from the bladder. This is commonly referred to as "obstruction," although the urethral lumen is only compressed. Resistance to urine flow requires the bladder to work harder during voiding, possibly leading to progressive hypertrophy, instability, or weakness (atony) of the bladder muscle. BPH involves hyperplasia (an increase in the number of cells) rather than hypertrophy (a growth in the size of individual cells), but the two terms are often used interchangeably, even among urologists.[15] Somewhat less commonly, BPH nodules may be found in the peripheral zone, which may be palpable with digital rectal examination, and are typically composed of epithelial glandular elements.[16] Moreover, McNeal (1990) pointed out that the landmarks of BPH were the budding and branching of epithelium glandular tissue from pre-existing ducts.[17] In fact, the increase in prostate volume seen with BPH is caused by cellular hyperplasia and reduced apoptosis. Stereological analysis indicates that the relative volume of stroma in macro-nodular BPH is increased 33% over that in the normal prostate.[18] According to Bostwick's and his colleagues study (1992), the presence of enlarged, hypertrophic basal cells; the increase in stromal mass, an enhanced extracellular matrix deposition, and reduced elastic tissue,[19] could ultimately constricts the urethra and leads to symptomology known in the medical field as lower urinary tract symptoms (LUTS),[13] that include bladder storage symptoms such as nocturia, urgency, increased urinary frequency, and difficulty starting the stream of urine; decreased urinary flow and incomplete emptying are generally attributed to problems with bladder emptying.[20] As BPH disease progresses, it is often associated with decreased urinary flow, worsening urinary symptoms and long-term complications.[21,22] Moreover, clinical BPH causing bladder outlet obstruction (BOO).[2] I fact, BPH represents the most common urologic disease among elderly men.[23]

Autocrine and paracrine growth factors are considered to be the factors that directly mediate enlargement of the prostate. Many of these growth factors are at least partly regulated by sex steroids.[24] Despite the obvious importance of BPH as a major health problem, little is known in terms of the biological processes that contribute to the pathogenesis of BPH. Although the exact etiology of BPH is unknown, it is thought to arise as a result of epithelial- stromal interactions in a certain hormonal milieu.[25]

Role of Inflammation

Inflammation is the basic process whereby tissues of the body respond to injury. The role of inflammation in prostate pathologies is suggested by the presence of

several kinds of inflammatory cells within the normal gland, as well as in patients with BPH and prostate cancer.[26] Prostatic inflammation is very common in BPH patients. Histological studies of BPH tissues have detected inflammatory cell infiltrates of varying densities in 30%- 50% of the cases.[27] Markers of inflammation such as the C-polysaccharide reactive protein (CRP) were also found to be upregulated.[28] Other factors such as Prostaglandin-end peroxide synthase 2 (COX)-2 have also been found to be upregulated.[29] COX-1andCOX-2 are the two isoforms of cyclooxygenase, which convert arachidonic acid (AA) into several eicosanoids such as prostaglandin,[30] which have various roles in mediating and moderating inflammation and are associated with the progression of BPH.[31] While Thromboxanes and prostacyclin, participate in several normal Physiologic processes and inflammation, COX-1 is constitutively expressed in most tissues.[30] Matsuyama *et al*., 2004[32] have observed that 5and 12-LOX were present in low amounts in BPH and normal prostate tissues. Wang *et al*., 2004[30] also found cyclooxygenase 2 (COX-2) in prostates with significant inflammation. McDowell *et al*., 2009,[33] improved that the inflammatory cells can be attracted to the prostate tissue microenvironment and can selectively promote the proliferation of prostate epithelial cells. Immigration of T cells into the prostate tissue is attracted by increased production of proinflammatory cytokines such as IL-6, IL-8 and IL-15.[34] These infiltrating cells are also responsible for the production of cytokines (IL-2 and IFNγ) which may support fibromuscular growth in BPH.[35] Steiner *et al*., 2003[36] study the expression and function of proinflammatory interleukin IL-17 and IL-17 receptor in normal and benign hyperplastic observed that the secretion of IL-17 leads to increased downstream production of the cytokines IL-6 and IL-8. Jose *et al*., 2009[37] also studied pro-inflammatory cytokines, and prostatic pathology (Benign prostatic hyperplasia and cancer) relationship with malignancy and revealed that IL-1a in epithelial cells seems to be involved in increased cell proliferation associated with BPH and Cancer. In patients with elevated expressions of IL-1α had also elevated prostate-specific antigen (PSA) levels (PSA>20ng/ml). These finding suggest that in both BPH and prostate cancer (PC), high expressions of IL-1α in epithelial cells may be related to cell proliferation and high PSA levels. In fact, IL-1α was expressed in 56% of BPH and 70% of PC patients. In addition, another cytokines including IL-12, and IL-23 were found to be secreted by stromal cells of prostate gland.[38]

Many recent reviews on the pathogenesis of BPH have provided evidence that strongly suggests a role of inflammation in the propagation of histological BPH.[4] Kramer 2006.[31] have recently proved the influence of inflammation on the pathogenesis of BPH. However, chronic inflammatory infiltrates, is mainly composed of chronically activated T cells and macrophages frequently are associated with BPH nodules.[4] Based on the available scientific evidence, it is highly likely that age-dependent weakening of the immune system, coupled with modified hormonal secretion, leads to the deterioration of a postulated population of suppressor cells that actively suppresses the recognition of prostatic antigens which leads to gradual infiltration of the prostate by lymphocytes and subsequent cascade of events that leads to BPH.[39]

Apoptosis in the development of BPH

The unique prostatic cellular phenotypes are induced and maintained by interaction between epithelium and adjacent stroma through intimate intercellular signaling pathways. Maintenance of cell and tissue homeostasis is dependent upon the dynamic balance of cell proliferation, differentiation, and apoptosis through interactions between cells and their microenvironment.[40]

Apoptosis (or programmed cell death) refers to the death of cells that occurs as a normal and controlled part of the growth of an organism. Apoptosis is currently considered a genetically encoded, ubiquitous pathway, enabling cells to undergo highly regulated cell death in response to specific signaling, which, along with its intracellular effectors, have been largely investigated.[41] A reduced rate of apoptosis has an important role in the etiology of BPH in the human prostate gland.[42] Many substances including cytokines, chemokines, growth factors, reactive oxygen and nitrogen species**,** all of these factors can have detrimental effect in the processes of cell proliferation, cell cycle control, and apoptosis.[43] Kyprianou *et al.*, 1996[44] studied the apoptotic versus proliferative activities in BPH improved that the tissue growth is depends upon a complex balance between the rates of cell proliferation and cell death (apoptosis). Disruption of the molecular mechanisms that regulate these two processes may underline the abnormal growth of the gland leading to BPH. Quantitative analyses, comparing BPH and normal prostatic tissues, have revealed that the total increase in both stromal and epithelial cells is a result of reduced apoptotic activity in parallel with increased cell proliferation.[45]

Prostatitis

There are no clear triggering events leading to BPH. Several studies have demonstrated the presence of heterogeneous bacterial and viral strains in BPH specimens, may lead to a production of proinflammatory cytokines and chemokines by BPH stromal cells, which may lead to prostatic growth.[13] Bacterial and noninfectious chronic prostatitis could be considered the pathogenetic background of hyper proliferative cellular pathways, possibly as a consequence of autoimmune responses against self-antigens released following tissue injury.[46]

Clinical prostatitis can be divided into acute and chronic bacterial prostatitis, which is caused by the growth of bacteria normally found in prostatic fluid, such as *Escherichia coli* and *Klebsiella*. Acute bacterial

prostatitis is caused by bacteria which are the least common form of prostatitis and it can be life-threatening if the infection is not treated, while chronic bacterial prostatitis is mainly caused by prostate stones or BPH and considered as a common cause of frequent urinary tract infections in men. On the other hand chronic non-bacterial prostatitis (chronic pelvic pain syndrome) is an inflamed prostate without bacteria.[47] Prostatitis can affect men of any age, and it is estimated that 50% of men experience the disorder during their lifetime. Moreover prostatitis is the most common urological disorder in men over the age of 50 and the third most common disorder in men younger than 50. According to the National Institutes of Health (NIH), prostatitis accounts for 25% of patients involving the genitourinary system by young and middle-aged men,[48] symptoms of prostatitis including: dysuria (painful urination), the feeling of urgently needing to urinate, frequent and painful urination, painful ejaculation, lower back pain, perineal pain (pain at the base of the scrotum and penis), chills, fever, muscular pain, and general lack of energy. Bacterial prostatitis may be divided into several categories according to the 1999 NIH Classification,[2] I: Acute prostatitis (bacterial); II: Chronic bacterial prostatitis; III: Chronic prostatitis/chronic pelvic pain syndrome: Subdivisions of III a (inflammatory) and III b (non-inflammatory) exist based on levels of pus cells in prostatic secretions, IV: Asymptomatic inflammatory prostatitis.

Serum PSA indicates BPH disease risk

Prostate-specific antigen (PSA), also known as gamma-seminoprotein or kallikrein-3 (KLK3), is a glycoprotein enzyme encoded in humans by the KLK3 gene. PSA is a member of the kallikrein-related peptidase family and is secreted by the epithelial cells of the prostate gland. PSA is produced for the ejaculate, where it liquefies semen in the seminal coagulum and allows sperm to swim freely.[49] It is also believed to be instrumental in dissolving cervical mucus, allowing the entry of sperm into the uterus.[50] PSA is present in small quantities in the serum of men with healthy prostates,[51] but its levels have been increased with prostate volume and directly related to patient age. Roehrborn *et al*., 1999,[52] showed that PSA predicted a prostate volume of 30 ml or greater with excellent sensitivity and specificity. Furthermore serum PSA is a valuable index of BPH disease risk. After prostate cancer is excluded PSA is a reasonable clinical surrogate marker for prostate volume. Men with large prostate glands have high PSA and are at increased risk for BPH disease progression,[53] PSA represented as greater than 1.3 ng /ml, 1.5 ng /ml and 1.7 ng /ml for men with BPH in their 50s, 60s and 70s, respectively. These criteria had 70% specificity and 65% to 70% sensitivity for detecting men with prostate volume exceeding 35 ml.[52]

Hormones in the BPH

Androgen plays a crucial role in development of BPH and prostate cancer (PC). Although androgen is essential for prostate development and growth, a number of experimental reports have suggested direct effects of estrogen on processes in this gland, including imprinting during the neonatal period and prostate hyperplasia and dysplasia.[54] Cunha *et al*., 2004,[55] demonstrated that androgen regulation and paracrine interactions were necessary for prostate glandular development and maintenance, establishing the key role of stromal-epithelial cell interactions in the prostate. A hormonal etiology involving dysregulation of stromal-epithelial cell interactions is recognized as important for BPH development, but the precise pathogenesis remains to be elucidated.[3] In 1895, White first documented the use of androgen ablation in 111 men with prostate hypertrophy treated by castration,[56] these early attempts to treat enlarged prostates with castration established the critical role of androgens in the maintenance of BPH. This series claimed success rates of approximately 80%, but did not distinguish among patients with BPH and advanced prostate cancer.[57] David and colleagues isolated testosterone in 1935 and in 1941, Huggins and Hodges introduced androgen deprivation as therapy for advanced prostate cancer. In the 1950s, retrospective analyses provided data suggesting that patients treated with hormonal therapy in the form of estrogens or orchiectomy demonstrated a survival and quality-of-life advantage when compared with patients followed in the pre-therapy.[56]

Androgens affect gene expression in a wide variety of tissues and cell types by binding with the androgen receptor (AR), which functions as a hormone-inducible transcription factor that is a member of the nuclear hormone receptor superfamily.[58]

Role of estrogen in BPH

Estradiol-17β (E2) is considered the most potent estrogen in men and is important for a variety of physiologic processes including bone maturation and mineralization, peak bone mass, and skin and lipid metabolism. In men, the majority of circulating E2 is formed from aromatization of testosterone (T), mainly in fat and muscle, while up to 20% is secreted by Leydig cells of the testes.[59] As men age, the intra-prostatic estradiol concentration increases or remains constant while the androgen concentration decreases. There is a strong correlation between the increasing estradiol: 5a-dihydrotestosterone (DHT) ratio and stromal hypertrophy.[60] Takase *et al*., 2006 [61] have detected estrogen receptors and enzymes involved in estrogen metabolism in human prostates. Although the role and mechanism of estrogens in the prostate is still unclear, there is growing evidence that estrogen could modify prostate growth and differentiation. An estrogen dominant is speculated to increase the production of androgen receptors and thus encouraging prostatic growth by sensitizing the prostate to androgen.[62] The current hypothesis may illustrate that the prostate locally produces estrogens to modulate the activity of epithelial and stromal cells. Moreover, aromatase gene (CYP19) is

regulated by a promoter (PII), which is responsive to inflammatory cytokines.[63] An increase in aromatase expression increases local estrogen levels that may lead to an increase in prostatic proliferation. Estrogens were found to stimulate DNA synthesis and induce metaplastic epithelial morphology in human.[64]

Androgen/ estrogen interaction in BPH

For many years the synergism between estrogen and androgen has been hypothesized as a mechanism to induce BPH. Estrogens are produced in the male by aromatization of rostenedione (forming estrone) or testosterone (forming estradiol).[65]

Hormone imbalance associated diseases can originate purely as a disorder of a gland or as a consequent of changing hormonal status of an organ due to factors such as age and environmental influences.[4] In fact men produce testosterone, a male hormone, and small amounts of estrogen (E2), a female hormone. As men aged, the amount of active testosterone in their blood decreases, which leaves a higher proportion of estrogen. In humans, BPH is known to be linked with both serum estrogen levels and urinary estrogen content.[66] Estrogens also exert local effects in the prostate via paracrine mechanisms. Aromatase, the enzyme required for metabolism of androgens to estrogens, is expressed in the stroma of the normal prostate.[67] Thus, local estrogen signaling, which affects both epithelia and stroma, is paracrine in nature. Estrogens directly induce aberrant proliferation in the basal layer of the prostate epithelium. This causes amulti-layering of the basal cells and results in sequamous metaplasia (SQM).[68] A pivotal role for estrogen in prostate inflammation is evident from previous studies on estrogen action using the hypo-gonadal (hpg) and ArKO mouse models. When exposed to estradiol for 6 weeks, it has been shown that mature hpg mice demonstrate a proliferative response within the prostatic stroma and epithelium. In addition to this response, neutrophils identified in the stroma were shown to migrate through the epithelium to the lumen which is distended as a result of accumulated cellular debris.[69] Furthermore, the biochemical and morphometric difference of BPH tissue from normal prostatic tissue suggests that an increased total number of cells cannot be the only mechanism operating in the pathogenesis of BPH. An abnormally increased total number of cells would only result in an enlarged prostate.[70] Prostatic conversion of T to E2 or of rostenedione to estrone also could contribute to higher prostate concentrations of estrogen. Aromatase mRNA can be detected by RTPCR technique in most BPH specimens. Stromal, but not epithelial, tissue levels of E2 and estrone increase with age, resulting in a very significant increase in the estrogen/androgen ratio in the stroma.[71]

Dihydrotestosterone (DHT)

Among androgens, 5a-dihydrotestosterone (DHT) is more potent than testosterone in maintaining certain characteristics of the prostate because DHT has a higher binding affinity for the androgen receptor and a two-fold to ten-fold higher potency in inducing transcriptional than testosterone.[72] DHT is the predominant androgen bound to the AR in the nuclei of target cells in the prostate. T is converted to DHT in the prostate by the enzyme steroid 5a-reductase type II (SRD5A2). The effects of androgen are mediated by AR, a member of the steroid-thyroid-retinoid superfamily of nuclear receptors. Binding of hormone is followed by dissociation from heat shock proteins, phosphorylation, dimerization, and binding to specific DNA sequences within or adjacent to androgen-responsive genes. The ligand-activated receptor regulates transcription of androgen-dependent genes.[73] Some research have been improved that even with a drop in blood testosterone levels, older men continue to produce and accumulate high levels of DHT in the prostate. This accumulation of DHT may encourage prostate cells to continue to grow. Scientists have noted that men who do not produce DHT do not develop BPH.[66] DHT appear to be implicated in the development and/ or maintenance of BPH.[74]

Testosterone and DHT bind with different affinities to the AR. This difference in binding affinity results in different levels of AR activation and therefore distinctive effects.[75] DHT stimulates glandular epithelium growth in the prostate and it is the major cause of rapid prostate enlargement that occurs between puberty and young adulthood. Despite an overall decline in testosterone levels as men aged, the prostate is still able to synthesize similar quantities of DHT. It is therefore hypothesized that the changes in the equilibrium between testosterone and DHT may lead to an increase in prostatic growth.[4] There is also a strong correlation between the increasing estradiol: DHT ratio and stromal hypertrophy.[60] Elevated DHT levels have been linked to BPH and PC.[76] DHT stimulates several growth factors that drive cellular proliferation in the human prostate, including growth-stimulatory epidermal growth factor (EGF), keratinocyte growth factor (KGF) and insulin like growth factors (IGFs). The activity of transforming growth factor-β (TGF-β), which modulates apoptosis, is also affected by DHT.[77]

Prolactin

Prolactin (PRL) is one of the non-androgenic hormones and growth factors that have been implicated in the etiology of BPH. Both the PRL ligand and its receptors are normally expressed in human and rodent prostate.[78] PRL also known as lactogen or mammotropin, is a polypeptide hormone secreted by the acidophilic lactotroph cells located in the adenohypophysis of the pituitary gland.[79] The first observation related to prolactin was made in 1928 by Stricker and Grueter. PRL was originally isolated and purified from the pituitary gland due to its mammopoietic and lactogenic properties.[80]

PRL binding sites have been identified in almost every tissue and cell type of adult mammals.[80] PRL gene expression has been confirmed in various regions of the brain, decidua, myometrium, lacrimal gland, thymus, spleen, circulating lymphocytes, and lymphoid cells of bone marrow, mammary epithelial cells and tumors, skin fibroblasts, and sweat glands. PRL can thus be found in several fluid compartments in addition to serum, such as cerebrospinal fluid, amniotic fluid, tears, milk, follicular fluid, and sweat.[81]

PRL is now recognized to exert a multitude of physiological functions in addition to its classical roles in lactation and reproduction. Currently, more than 300 distinct biological activities of PRL have been identified.[82] It has long been thought that prolactin influences normal growth, development and function of prostate.[83] The synthesis and secretion of PRL by lactotrophic cells in the anterior pituitary gland is subjected to multiple regulators. These can broadly be classified as endocrine, paracrine, juxtacrine or autocrine, depending on their respective origin. The secretory activity of the lactotrophs reflects a balance between local and distant inhibitory and releasing factors. In the absence of target gland hormones to provide feedback control over the lactotrophs, PRL also to some extent auto regulates its own release.[84] The gene encoding human PRLR is located on chromosome 5 and contains at least 10 exons, with an overall length exceeding 100 k.[80] PRL and other hormones hyper secreted in stress situations have been implicated in prostate growth and proliferation,[85] and in the development and regulation of BPH and PC.[86,87] The concept of PRL regulation of target tissue size by controlling not only proliferative activity but also programmed cell death is relatively new. PRL has been reported to suppress apoptosis in several target tissues, including hematopoietic cells, prostate and mammary gland, but also to induce cell death in the corpus luteum.[88] Concerning the prostate gland, an in vitro study by Ahonen *et al*., 1999[89] has demonstrated that PRL can significantly inhibit apoptosis in androgen deprived dorsal and lateral rat prostate cultures, as assessed by nuclear morphology and in situ DNA fragmentation analysis. Conflicting data exist on changes in PRL levels with increasing age.[90] Alterations in neuroendocrine control mechanisms regulating secretion are also known, usually resulting in modestly elevated PRL levels. Pharmacotherapy interfering with generation and action of dopamine is one cause of PRL alterations.[91] Indirect evidence of possible PRL involved in the development of BPH and/or carcinoma has come from reports that circulation hormone level were significantly higher in older men when compared with those found in younger males.[92]

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