Aging of the male reproductive system

M. Hermann, G. Untergasser, H. Rumpold, P. Berger*

Institute for Biomedical Aging Research, Austrian Academy of Sciences, Innsbruck, Austria

Received 4 June 2000; received in revised form 15 June 2000; accepted 15 June 2000

Abstract

Reproductive and sexual physiology, changes in body composition and mental performance in the aging male cannot simply be reduced to presumptive hypogonadism defined by low androgen serum levels or by decreasing levels of growth hormone (GH) and melatonin. Morphological changes in organs at different regulatory levels of hormonal networks governing, for example reproduction, such as diminished hypothalamic pulse generator mass, focal degeneration and loss of Leydig cells in testicular tissue, lead to diminished reserve capacities in production and to loss of coordinated pulsatile release of hypothalamic neuropeptides (e.g. gonadotropin releasing hormone, GnRH) and consequently diminished release of pituitary protein and glycoprotein hormones and testicular steroid hormones. Owing to presumptive alterations in feedback sensitivity, decreased testosterone levels do not necessarily upregulate pituitary LH secretion. Alternatively, increased serum levels of LH and FSH can be observed in old men either because of primary hypogonadism or to decreased hypothalamic opioid tone. In general, endocrine functions are sufficient to maintain fertility in elderly men because, except for sperm motility, quantitative and qualitative functional semen parameters are apparently not affected by age. Nevertheless, reduced endocrine and organic functions might become critical at different levels, with high inter-individual variability, of the hypothalamo/pituitary/gonadal-axis. One of the most intriguing organic manifestations of male aging is benign prostatic hyperplasia (BPH), the pathologic prevalence of which closely matches age. Age-associated changes in the endocrine system and in local networks of epithelial, stromal and luminal factors may play important roles in BPH development. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Aging; Male; Fertility; Testosterone; Growth hormone; Prostate; Testis; Reproduction

1. Introduction

Progress in preventive and therapeutic medicine, such as vaccination or the advent of antibiotics, has dramatically increased the average life expectancy of both genders in most industrialized countries. This progress, however, is unfortunately paralleled by age-associated...
morbid and premorbid changes in function, such as prostate hyperplasia (BPH), osteoporosis or general frailty, that limit free and independent life for elderly men (reviewed by Bakshi and Miller, 1999). As a consequence, a major task of modern society is not merely to extend life, but to also ensure the independence and health of this aging population, thereby increasing the quality of life and, as a byproduct, lowering the costs of care for the elderly.

Acquired hypogonadism of the aging male is not well defined because of the lack of age-adjusted reference values and its unclear pathophysiological consequences. Lower androgen serum levels of elderly men are not linked to a cessation of reproductive capacity (reviewed by Gooren, 1996; Plas et al., 2000), which distinguishes male aging from female menopause, where unequivocal cessation of reproductive capacity coupled to loss of gonadal endocrine function is observed. Primary testicular age-related dysfunction with regard to diminished androgen production or spermiogenesis might be reflected by a rise in gonadotropin serum levels, similar to female menopause. The proportion of such cases seems to increase with age and to contribute to the statistically significant overall increase in serum FSH and LH of elderly men (Gray et al., 1991; Madersbacher et al., 1993). On the other hand, a secondary drop of sex steroid serum levels, despite sufficient testicular and pituitary reserves of production capacities and loss of circadian rhythmicity (Bremner et al., 1983), are because of decreased masses of releasing hormones (GnRH) at each hypotalamic pulse and an age-associated loss of neurohormone synchrony of the hypotalamic pulse generator followed by lower amounts of released pituitary gonadotropins (reviewed by Gooren, 1996; Veldhuis et al., 2000).

Aging male characteristics develop in a triangle of morphological changes in organs, partially coupled to endocrine networks and fertility. These highly variable individual characteristics seem to be strongly influenced by lifestyle and environmental factors. Despite the above-mentioned variability, the majority of elderly men suffer from BPH.

Herein we present an overview of age-associated changes in the male reproductive system, hormonal networks and their most important consequence: The age-associated growth of the prostate leading to BPH in elderly men. A major focus will be on the three regulatory levels of prostatic growth and differentiation, involving luminal factors necessary for optimal fertility, but acting for decades in a retrograde fashion.

2. Age-related changes in the hypothalamic, pituitary, gonadal axis

Testosterone (T) and, to a greater extent, free T and bioavailable or weakly bound T (albumin-bound T) decline with age in men (reviewed in Morley and Perry, 1999; Hermann and Berger, 1999), as shown by a decrease of ±35% of total and of 50% of free T levels between the ages of 20 and 80. Plasma levels of bioavailable T below the lower normal limit (<70 ng/dl) occur in 7% of elderly men in the age group 40–60, 20% are affected in the age group 60–80 and 35% in the age group over 80 years old (reviewed by Vermeulen and Kaufman, 1995).

There is no clear consensus about the causative mechanism of this rather modest age-associated decline, which may originate from all three levels of the
### Table 1
Age related reproductive hormonal changes in men

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Serum levels in young men</th>
<th>Serum levels in old men</th>
<th>Age (years/o)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>↓ 11.51 nmol/l</td>
<td>10.27 nmol/l</td>
<td>40/70</td>
<td>Gray et al., 1991</td>
</tr>
<tr>
<td>Free T</td>
<td>↓ 0.23 nmol/l</td>
<td>0.16 nmol/l</td>
<td>40/70</td>
<td>Gray et al., 1991</td>
</tr>
<tr>
<td>DHT</td>
<td>= 0.85 nmol/l</td>
<td>=</td>
<td>40/70</td>
<td>Gray et al., 1991</td>
</tr>
<tr>
<td>Estradiol</td>
<td>= 96 pmol/l</td>
<td>=</td>
<td>40/70</td>
<td>Gray et al., 1991</td>
</tr>
<tr>
<td>SHBG</td>
<td>↑ 26.2 nmol/l</td>
<td>37.9 nmol/l</td>
<td>40/70</td>
<td>Gray et al., 1991</td>
</tr>
<tr>
<td>DHEA</td>
<td>↓ 22 nmol/l</td>
<td>5 nmol/l</td>
<td>20–30/70–80</td>
<td>Labrie et al., 1997</td>
</tr>
<tr>
<td>DHEAS</td>
<td>↓ 12 μmol/l</td>
<td>3 μmol/l</td>
<td>20–30/70–80</td>
<td>Labrie et al., 1997</td>
</tr>
<tr>
<td>FSH</td>
<td>↑ 619 ng/l;</td>
<td>1948 ng/l</td>
<td>27 ± 4/72 ± 3</td>
<td>Madersbacher et al., 1993</td>
</tr>
<tr>
<td>LH</td>
<td>↑ 3.67 IU/l</td>
<td>6.65 IU/l</td>
<td>40/70</td>
<td>Gray et al., 1991</td>
</tr>
<tr>
<td>Free GPHalpha</td>
<td>↑ 142 ng/l</td>
<td>279 ng/l</td>
<td>27 ± 4/72 ± 3</td>
<td>Madersbacher et al., 1993</td>
</tr>
<tr>
<td>GH</td>
<td>↓ 20 ng/ml</td>
<td>3.2 ng/ml</td>
<td>20–29/60–79</td>
<td>Rudman et al., 1981</td>
</tr>
<tr>
<td>Prolactin</td>
<td>= 6.8 μg/l</td>
<td>6.06 μg/l</td>
<td>40/70</td>
<td>Gray et al., 1991</td>
</tr>
</tbody>
</table>
hypothalamo-pituitary–testicular axis (reviewed in Gooren, 1996; Hermann and Berger, 1999; Morley and Perry, 1999).

Decreased numbers of Leydig cells (Neaves et al., 1984), impaired testicular perfusion (Suoranta, 1971) and reduced release of T upon stimulation by hCG (Harman and Tsitouras, 1980) support a primarily testicular cause of lower serum T levels, i.e. primary hypogonadism. In addition, it has been shown that the LH levels are elevated in response to the decline of T levels with aging (Deslypere and Vermeulen, 1984), although these levels are lower than those observed in younger men with similarly decreased T levels (Korenman et al., 1990). Rarely do the LH serum levels of elderly men rise outside of the normal, suggesting that the changes are predominantly because of an alterations in functions of the hypothalamic–pituitary unit, i.e. secondary hypogonadism. Interestingly, in men very old men (>80), elevated LH levels are not unusual, perhaps due to a decrease in their opioid tone, since endogenous opioids suppress the release of GnRH and therefore LH (reviewed by Morley and Perry, 1999).

Hypothalamic impairment of stimulating LH and subsequent androgen secretion is inferred from the loss of circadian rhythm of LH and T levels (Bremner et al., 1983; Pincus et al., 1996). The nycthemeral variations in plasma T levels are significantly decreased in elderly men (Deslypere and Vermeulen, 1984). The reduced number of spontaneous high amplitude LH pulses in elderly men does not seem to be a consequence of a decreased sensitivity of the gonadotrophs to LHRH, but rather may be the consequence of the release of smaller amounts of LHRH at each pulse (Kaufman et al., 1991).

In addition to aging per se, other hereditary, environmental (obesity, stress), psychosocial (depression, smoking, drugs) or socio-economical (diet, hygiene) factors may influence serum T levels in elderly men, resulting in even lower circulating T levels (Vermeulen and Kaufman, 1995). Age related hormonal changes in men are summarized in Table 1.

3. Fertility

An important issue in the process of male aging is the maintenance of fertility (reviewed by Plas et al., 2000): while female fertility ends at the entrance into menopause around the age of 50, men do not show such an unavoidable and clear-cut cessation of reproductive capacity. Nonetheless, increasing life expectancy, in conjunction with a trend towards higher maternal and paternal ages and improvements in assisted reproduction, especially intracytoplasmic sperm injection (ICSI), have renewed interest in the issue of male fertility with advancing age.

In this context, it is important to discriminate between healthy aging males without concomitant diseases and those with chronic illnesses that significantly influence male gonadal function (Turner and Wass, 1997).

There are several age-associated histomorphological alterations of the testis, such as accumulation of the "aging" pigment lipofuscin in Leydig cells (Sasano and Ichijo, 1969), thickening and hernia-like protrusions of the basal membrane causing a dilation of the tubuli seminiferi and fibrotic thickening of the tunica albuginea of the testis by approximately 30% (Johnson et al., 1984), reduced testicular perfusion (Sasano and Ichijo, 1969; Suoranta, 1971) and reduced number of Leydig cells, which produce T (Neaves et al., 1984) (Table 2).
Consequences on spermiogenesis of the above-mentioned morphological alterations are not easily delineated due to the lack of data and the high intra-individual variations of spermiograms. Although in autopsy studies, a reduction of spermiogenesis was reported to be more evident in men over 40 as compared to younger men (Sasano and Ichijo, 1969), classical parameters of spermiograms, i.e. semen volume, sperm count, total number of spermatozoa, do not change significantly with age, as shown in fertile young fathers (24–37 year) and elderly fertile men (60–88 year) (Nieschlag et al., 1982). The only semen-parameter that seems to decline with age is sperm motility (Nieschlag et al., 1982; Haidl et al., 1996), which could also be due to increasing latency periods, since aging is related to decreased frequencies of intercourse.

Functional parameters, like the fertilizing potential or the acrosome reaction and chromatin condensation, do not differ between young and elderly men (Nieschlag et al. 1982; Haidl et al., 1996).

Although there is no correlation in numerical aberrations, the frequency of structural chromosomal abnormalities in spermatozoa positively correlates with increasing paternal age. The percentage of spermatozoa showing structural abnormalities is 2.8% in men aged 20–24 year, and increases 4-fold to 13.6% in men over 45. The increased frequency of structural abnormalities may be secondary to prolonged exposure of germ cells to mutagens (Murray and Meacham, 1993). Paternal ages of more than 40 years were associated with a 20% greater chance of birth defects, as in 20-year old fathers, which increased by another 10% in paternal ages of 50 years (Friedman, 1981). The American Fertility Society has expanded its guidelines on the use of donor semen for intrauterine insemination by recommending an age limit of 50 years or less for semen donors to reduce the risk of potential structural or autosomal dominant genetic abnormalities (Bordson and Leonardo, 1991).

4. Regulation of growth in the aging prostate

4.1. General and developmental aspects

The prostate as the target organ of the hypothalamic-pituitary–testicular axis is closely connected to the endocrine network and to reproduction. Growth of the prostate in elderly
Men leads to the most common and costly age-related disease, i.e. benign prostatic hyperplasia (BPH). In autopsy studies, this can be detected in almost 80% of the male population by the age of 80. Twenty-five percent of elderly men suffering from BPH will require medical treatment to alleviate urinary obstruction (National Kidney and Urological Disease Advisory Board, 1990). In addition to expensive surgical treatment, therapeutic interventions interfering with sex steroid hormone metabolism with 5α-reductase inhibitors have been developed, but the benefits are limited. Aromatase inhibitors did not show significant effects on BPH in clinical trials (Marcelli and Cunningham, 1999).

Age-related increase in prostate volume is caused by cellular hyperplasia of basal cells of the acinus and of stromal cells, i.e. smooth muscle cells and fibroblasts. Quantitative morphometric analysis of symptomatic BPH patients compared to healthy controls...
revealed a 33% increase in stromal volume (Shapiro and Steiner, 1996). Moreover, apoptosis of stromal cells is reduced, and lifespan of BPH stromal cells exceeds 30 years. Although mean proliferation indices of epithelium and stroma are quite similar, and epithelial cells regularly undergo programmed cell death, no apoptotic cells can be detected in the stroma (Claus et al., 1997), providing evidence that changes in the epithelium/stroma ratio occur during the development of BPH.

Embryonic, pubertal and age-related prostatic growth is mainly governed by hormonal networks at different levels: Three regulatory levels affecting prostatic growth and function can be discerned, comprising endocrine factors (sex steroid hormones and pituitary-derived protein hormones), local factors acting in auto/paracrine manners between epithelial and stromal cells (fibroblast growth factors, FGFs, insulin-like growth factors, IGFs, epidermal growth factor, EGF) (Shapiro and Steiner, 1996), and finally luminal factors (zinc, kallikreins, prostaglandins and others) originally needed for optimal fertility but at the same time acting in a retrograde manner on the prostate of aging males. Changes of those factors in their absolute and relative concentrations are considered to favor proliferative disorders of the prostate by altering the balance of cell growth and death. The following will give a brief overview on molecular growth regulatory networks of the prostate (Fig. 1).

4.2. Endocrine factors and prostatic growth

4.2.1. Sex steroids

Several hypothesis have been put forward to explain the development of BPH based on alterations of local sex steroid metabolism (reviewed by Marcelli and Cunningham, 1999). Growth and development of the prostate in puberty is primarily dependent on androgens, predominantly T and its most bioactive metabolite, dihydrotestosterone (DHT), which is generated locally by the 5\(\alpha\)-reductase II. Androgens are considered to have a role in the pathogenesis of proliferative disorders, since they do not occur in men castrated prior to puberty who do not receive subsequent androgen therapy. Estrogens seem to potentiate the effect of androgens; simultaneous administration of T and estrogens in dogs causes prostatic overgrowth, apparently by upregulation of the epithelial androgen receptor (AR) (Marcelli and Cunningham, 1999).

The estrogen hypothesis is based on the observation that the stroma of BPH patients compared to normal prostates contains higher concentrations of estrogens, presumably as a consequence of elevated aromatase activity (Kriigel et al., 1993). Further, it is conceivable that aromatase activity might be upregulated by FSH expressed by prostatic cells (Dirnhofer et al., 1998). The mRNA of aromatase was detected in prostatic tissue by reverse transcriptase–polymerase chain reaction (RT-PCR) and its level of expression did not change in BPH and PCa, as shown by Northern Blot analysis (Hiramatsu et al., 1997). Interestingly, decreased prostatic estrogen-receptor (ER) mRNA levels were observed with age (Bonnet et al., 1993), which might explain the poor efficacy of aromatase inhibitor therapies (Atamestane®) in the treatment of symptomatic BPH (Marcelli and Cunningham, 1999), although estradiol serum levels seem to correlate with BPH (Schatzl et al., 2000). Thus, it can be assumed that sex steroid hormones are important for
embryonic and pubertal prostate development, for epithelial cell renewal and secretory function, and also play a permissive role for prostatic growth after puberty.

4.2.2. Growth hormone/insulin-like growth factor I

Growth hormone (GH, somatotropin) is secreted by the pituitary subsequent to stimulus from the growth hormone releasing hormone (GHRH). GH stimulates the production of IGF-I that in turn, is responsible for growth of the target organs. The prostate, expressing the corresponding receptors, is responsive to both IGF-I and GH (Cohen et al., 1994; Untergasser et al., 1999). Systemic administration of GH to hypophysectomized immature rats increases prostatic weight, presumably, because of the upregulation of androgen receptor, IGF-I and IGF-I-R; whether the effect is primarily due to GH or to IGF-I (reviewed in Reiter et al., 1999) remains to be determined. A potential direct role of GH on prostatic growth was shown on an androgen-dependent prostate tumor cell line (LnCAP) and on prostatic smooth muscle cells, the proliferation of which is increased upon GH exposure (Untergasser et al., 1999) and blocked by GH antagonists (Reiter et al., 1999), consistent with the finding of enlarged prostatic sizes in acromegalic men (Colao et al., 1999).

4.2.3. Prolactin

PRL, the cognate molecule of GH, stimulates proliferation and differentiation of prostatic epithelial cells (Nevalainen et al., 1997; Reiter et al., 1999). Transgenic mice overexpressing Prolactin (PRL) show a 20-fold increase of prostatic weight (Wennbo et al., 1997), which can partially be explained by the stimulating effect of PRL on testicular steroidogenesis (Reiter et al., 1999).

Immunohistochemically, PRL receptors were found only in the secretory epithelium, basal epithelial cells were negative. In organ cultures, exogenous administration of hPRL increased DNA synthesis of epithelial cells. Additional effects of PRL on prostatic cells are stimulation of the mitochondrial aspartate amino-transferase and of the zinc uptake mechanism (Costello et al., 1999). Interestingly, androgen-dependent expression of PRL has been observed in rat prostatic epithelium in vivo and in organ culture, suggesting a role as an auto/paracrine factor (Nevalainen et al., 1997).

4.3. Local factors

4.3.1. Insulin-like growth factor system

The human prostate contains all elements of the IGF network (IGF-I and -II, IGFBP-2, -3 and -4, IGF-R). IGF-I is predominantly found in prostatic epithelial cells, which also produce IGFBP-2, -3 and -4, whereas IGF-II is mainly expressed in stromal cells; the latter also produce IGFBP-2, -3 and -4 (Cohen et al., 1994). IGF-I receptors are present on epithelial cells (Cohen et al., 1994). Studies investigating the direct role of IGFs on prostatic cell growth showed proliferative effects that are negatively regulated by IGF-binding proteins (Sutkowski et al., 1999). An IGF-independent effect was shown for IGFBP-3 that was able to induce apoptosis and mediate the effect of TGFβ 1 (Rajah et al., 1997). Prostatic mRNA levels of IGF-I, IGF-II and IGF-I receptor have been studied in BPH patients compared to healthy control groups and young men. In contrast to normal
prostatic tissue of young men, IGF-I, IGF-II and IGF-I-R were significantly elevated in BPH tissue (Bonnet et al., 1993). Moreover, increases of PSA and kallikrein 2 (hK2) serum-levels have been reported in BPH and PCa patients (Recker et al., 2000). Kallikreins are known to activate EGF and NGF from their precursor molecules in epithelial cells, and to proteolytically cleave IGFBP-3, a proapoptotic gene product in prostate stromal cells (Sutkowski et al., 1999). Disturbances of the local balance of proliferative IGFs and antiproliferative IGFBPs may be involved in abnormal stromal growth of the prostate.

4.3.2. Epidermal growth factor/transforming growth factor α

Transcripts and proteins of these mitogenic factors and their common receptor are present only in epithelial cells of the prostate, suggesting auto-/paracrine functions (De Bellis et al., 1996). Notably, cells of prostate cancer in a progressive state switch from production of EGF to TGFα, contributing to growth and unrestrained proliferation (Seth et al., 1999).

4.3.3. Fibroblast growth factors

The source of FGFs in the prostate are stromal cells. All members of the FGF-family act in a paracrine fashion on epithelial cells and are autocrine mitogens for stromal cells. The predominant FGF transcript is FGF 7 (KGF), followed by FGF 2 and traces of FGF 1 (Ittman and Mansukhani, 1997). All FGFs are potent mitogens, especially for epithelial cells expressing FGFR I and II in higher amounts than stromal cells (Ittman and Mansukhani, 1997). Recently, FGF 9 and FGF 10 were expressed in prostatic stromal cells. Notably, BPH tissue has an increased transcription rate of FGF I receptors compared to normal prostatic tissue (Hamaguchi et al., 1995).

4.3.4. Transforming growth factor β

TGFβ 1 concentrations in seminal plasma are higher that in any other physiological biological fluid (Chu et al., 1996). In the prostate, it is predominantly produced in the basal cells of the acinus the corresponding receptors being expressed in epithelial cells, TGFβ RI in the basal and TGFβ RII in the secretory cells. In stromal cells, the staining-intensity for TGF and its receptors is much less (Royuela et al., 1998). From a functional point of view, TGFβ is a pleiotropic factor playing an important role in the regulation of growth and differentiation of prostatic cells (Lee et al., 1999) by inhibiting proliferation and inducing apoptosis. In prostatic stroma, it is responsible for smooth muscle cell differentiation, and thus, might be involved in the development of smooth muscle cell-containing nodules, characteristic of BPH (Lee et al., 1999).

Changes of prostatic TGFβ occurring in benign and malignant diseases are noteworthy; during malignant transformation, a loss of functional TGF R expression occurs accompanied by an increased TGFβ production. This loss of functioning receptors provides an advantage for growth to these cells. The increased local TGFβ concentration found in prostatic cancer tissue correlates to elevated production of extracellular matrix, increased angiogenesis and inhibition of host immune function (Lee et al., 1999).
4.4. Luminal/epithelial interactions

4.4.1. PSA, prostaglandins and zinc

Secretion of luminal proteins and low molecular weight factors could also be affected by age and contribute to the imbalance of cell growth and death in prostatic tissue. Factors originally needed for optimal fertility might, at the same time, influence prostate epithelial cell renewal and secretory function.

PSA is produced in prostatic epithelial cells after androgen stimulus. In addition to its clinical use as a screening marker for prostate carcinoma, this member of the kallikrein family plays a significant biological role in the liquefaction of seminal fluid by cleaving seminal-vesicle-derived semenogelins I and II. Moreover, PSA, as a serine protease, has been shown to cleave IGFBP-3, thereby interfering with the growth regulatory actions of the IGF axis (Plymate et al., 1996). This ability of PSA presumably accounts for the presence of IGFBP-3 fragments, in contrast to intact IGFBP-2 and -4 in human seminal plasma. Growth regulatory functions of PSA due to IGFBP-3 cleavage have been shown on prostatic cells (Sutkowski et al., 1999).

Moreover, age-related changes in concentrations of low molecular weight factors, such as of zinc and prostaglandins present in micromolar range in seminal fluid and their effects on epithelial cell growth and secretory function, remain to be analyzed.

The prostate contains the highest concentration of zinc of any organ in the human body. Zinc levels were shown to decrease in prostatitis (Fair et al., 1976) and in prostate carcinoma (Zaichick et al., 1997). Zinc uptake is influenced by androgens and PRL (Costello et al., 1999). From a functional point of view, zinc plays an important role in regulating citrate metabolism via inhibition of m-aconitase (Costello et al., 1999). Additionally, zinc inhibits cell growth of prostatic cancer cell lines, although whether this effect is mediated via necrosis (Iguchi et al., 1998) or apoptosis (Liang et al., 1999) is still under investigation, in our, and other, laboratories.

4.4.2. PSP 94 and GPH-α

Recently, it has been shown that the prostate-specific protein 94 (PSP 94), one of the predominant proteins found in the seminal plasma, can induce apoptosis in the PC 3 prostate cancer cell line (Garde et al., 1999). Further, the alpha subunit of glycoprotein hormones, which shares a common structural motif, the so-called “cystine knot”, with other protein growth factors, is present in vast amounts in seminal plasma, exceeding serum levels of 10 000-fold. It is secreted in an androgen-dependent manner by prostatic epithelial cells, and our own data suggest a growth inhibitory effect on prostatic smooth muscle cells, on the androgen independent (PC3) and the androgen independent (LnCAP) prostatic cancer cell lines (Rumpold et al., unpublished data). The biological significance of both molecules remains to be clarified.

In summary, the male reproductive system can be viewed as an interactive homeostatic network in which changes at different levels may occur during the course of aging. Depending on their origin, i.e. the hypothalamic GnRH pulse generator, the anterior pituitary gonadotropes or the steroidogenic cells in the testis, these changes may result in a loss of circadian rhythmicity as well as altered serum levels of hormones. Although these changes are far less drastic than those conferred by menopause in women, men show
highly age-related clinical symptoms, such as BPH, which may be a result of the above-mentioned changes in the homeostatic networks. Although these changes do not seem to be of clinical importance for the persistent fertility of aging men, they might be significant in the development of BPH, the etiology of which is largely unknown. Although proliferation and secretion of epithelial cells is under control of sex-steroid hormones, their serum levels cannot be correlated with the development of BPH. Thus, research has been focused on elucidating local prostatic networks of growth-stimulatory and inhibitory factors and their changes with age. Stromal-epithelial and epithelial-luminal interactions as a consequence of lifelong prostatic reproductive function might influence cell regulatory mechanisms leading to abnormal growth of stromal cells.

Acknowledgements

This work was supported by the Austrian Science Funds (P 13652-GEN). We would like to thank Drs Plas, Madersbacher and Dirnhofer for continuous collaboration and intensive discussions.

References


