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REVIEW

Preclinical therapy of benign prostatic hyperplasia with neuropeptide hormone antagonists

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Abstract

Benign prostatic hyperplasia (BPH) is a pathologic condition of the prostate described as a substantial increase in its number of epithelial and stromal cells. BPH may significantly reduce the quality of life due to the initiation of bladder outlet obstruction and lower urinary tract syndromes. Current medical therapies mostly consist of inhibitors of 5α-reductase or α1-adrenergic blockers; their efficacy is often insufficient. Antagonistic analogs of neuropeptide hormones are novel candidates for the management of BPH. At first, antagonists of luteinizing hormone-releasing hormone (LHRH) have been introduced to the therapy aimed to reduce serum testosterone levels. However, they have also been found to produce an inhibitory activity on local LHRH receptors in the prostate as well as impotence and other related side effects. Since then, several preclinical and clinical studies reported the favorable effects of LHRH antagonists in BPH. In contrast, antagonists of growth hormone-releasing hormone (GHRH) and gastrin-releasing peptide (GRP) have been tested only in preclinical settings and produce significant reduction in prostate size in experimental models of BPH. They act at least in part, by blocking the action of respective ligands produced locally on prostates through their respective receptors in the prostate, and by inhibition of autocrine insulin-like growth factors-Ⅰ/Ⅱ and epidermal growth factor production. GHRH and LHRH antagonists were also tested in combination resulting in a cumulative effect that was greater than that of each alone. This article will review the numerous studies that demonstrate the beneficial effects of antagonistic analogs of LHRH, GHRH and GRP in BPH, as well as suggesting a potential role for somatostatin analogs in experimental therapies.

Key words: Benign prostatic hyperplasia; Luteinizing

hormone-releasing hormone; Growth hormone-releasing hormone; Gastrin-releasing peptide; Somatostatin; Targeted therapy

Core tip: A new, effective treatment for benign prostatic hyperplasia (BPH) is critically needed. Present side effects of therapy include impotence, decreased libido, abnormal ejaculation, dizziness, weakness, blurred vision and insomnia. Preclinical data suggest that antagonists of neuropeptides growth hormone-releasing hormone, luteinizing hormone-releasing hormone and gastrin-releasing peptide are effective in shrinking prostates in part by suppressing growth factors and inflammatory cytokines. Their effect is exerted through a decrease in levels of circulating hormones and also on a direct action on their respective prostatic receptors. These analogs seem to have the same clinical effects as the currently available BPH medical therapies but possess greater efficacy and have fewer or no side effects.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is an age-dependent condition which may start as early as 40 years of age and its prevalence increases to 50%-60% in men in their 60's[1,2]. The BPH-associated growth in prostatic volume arises from the increase in epithelial and stromal cell number occurring mainly in the transition zone of the prostate[3]. In some cases, histologic BPH remains asymptomatic and the patient does not require clinical treatment. However, the prostate gland frequently becomes substantially enlarged, resulting in compression of the diameter of the urethra thus leading to bladder outlet obstruction[1]. Lower urinary tract symptoms (LUTS) that are often associated with BPH are developed in response to the increased resistance of the urethra and the consequently elevated pressure in the bladder[4,5]. Unfortunately, the current medical modalities aimed at treating BPH are not completely effective[6]. These include therapies targeting 5α-reductase activity to inhibit the production of dihydrotestosterone as well as compounds that reduce the adrenergic tone at the bladder outlet, these collectively known as α_1-adrenergic blockers[7-9]. When an intervention is required, either a minimally invasive technique (such as transurethral needle ablation or microwave thermotherapy) or surgery (transurethral resection of the prostate or "open prostatectomy") is performed to reduce the volume of the prostate and its restriction in outlet flow[10-12].

The pathogenesis of BPH is not completely understood although it has been suggested that a decrease in the rate of cell death is more critical for the hyperplastic behavior than a rise in cell proliferation[13]. Various factors, such as a discrepancy in androgen and estrogen levels[14-17], altered autocrine regulation by growth factors [most importantly fibroblast growth factors-2 (FGF-2) and FGF-7][18] or cytokines released by infiltrated inflammatory cells[19] have been found to contribute to the development of BPH. It has also emerged that mesenchymal transition of epithelial and endothelial cells directed by the transforming growth factor (TGF)-β/Smad pathway may play a key role in the pathogenesis of BPH[20]. Most recently, neuropeptide hormones were also found to play a major role in this process, not only by indirectly controlling their classical hormonal targets but also as local regulators in the prostate[21-25]. Consequently, their receptors became potential targets for the development of new treatment strategies for BPH. These include the potential therapeutic utilization of antagonistic analogs of luteinizing hormone-releasing hormone (LHRH), growth hormone-releasing hormone (GHRH) and gastrin-releasing peptide (GRP). The utilization of these analogs in experimental BPH also improved our knowledge on the physiological role of neuropeptides and their receptors in the pathogenesis of BPH. The blockade of these receptors by specific antagonists inhibits the proliferation of stromal and epithelial cells and reduces the release of cytokines and growth factors[6,20,22,24,25] indicating the participation of the native neuropeptides in these processes. As new antagonistic analogs of neuropeptides have recently become available for clinical practice as well others are currently being developed for human trials, we felt that a review of recent findings related to their use in BPH is timely. This review therefore focuses exclusively on preclinical and clinical studies where neuropeptide antagonists were tested against BPH. Additionally, the use of somatostatin agonists is also suggested based on previous findings in prostate cancer with the hope it will facilitate their experimental and clinical testing.

ANTAGONISTS OF LHRH

Initially, LHRH antagonists were developed for the purpose of contraception using reduction of the mid-cycle pituitary follicule-stimulating hormone and luteinizing hormone (LH) release thus preventing ovulation[26,27]. Early antagonistic analogs of LHRH demonstrated low potency and significant side effects due to a substantial histamine release[28]. Since those first attempts, many antagonistic analogs of LHRH have been synthetized with higher potency and greatly decreased histamine-releasing activity[29,30]. Cetrorelix[29] was the first antagonistic analog of LHRH that was approved for use in clinical practice as part of the hormonal therapy of *in vitro* fertilization used to prevent premature LH surges[31]. Numerous clinical trials have been conducted with Cetrotide brand of cetrorelix for the treatment of ovarian cancer, endometriosis, ovarian hyperstimulation syndrome and uterine

leiyomyoma[32-35]. Cetrorelix was also tested in patients with prostate cancer[36,37]. The most advanced LHRH antagonist, degarelix, that has been approved for patients with advanced prostate cancer has an improved formula that allows the slow tonic release of the peptide, and moreover, has the lowest histamine-releasing activity among the LHRH antagonists[38,39].

The utilization of LHRH antagonists in the treatment of BPH is suggested by several previous findings. Hormonal therapy with the 5-α reductase inhibitors has long been used to treat BPH and has been shown to shrink prostate volume and improve urinary outflow[16]. This suggests a dihydrotestosterone-dependent pathology of the disease. However, only 30%-50% of patients respond to this treatment[40] highlighting the need for the development of a more effective intervention, such as a systematic suppression of testosterone levels. Cetrorelix (300 μg) was able to reduce serum testosterone levels by 80% at 12 h after administration in men with a mean age of 24[41]. This finding encouraged the clinical testing of cetrorelix in BPH.

In a study by Gonzalez-Barcena *et al*[36], 11 patients were recruited with symptomatic BPH. Subjects were treated with 500 μg cetrorelix every 12 h for 4 wk in an open label study. Improvements were seen in urinary flow just after the first week of treatment and it became normal after 4 wk. Also, the level of serum acid phosphatases reached normal levels at the end of treatment. Free testosterone levels either dropped immediately after the first cetrorelix injection or decreased gradually throughout the 4 wk, however, in 4 patients it remained similar to pretreatment values. In all cases, prostatic volume decreased significantly which suggests a testosterone-independent action of cetrorelix on the prostate in patients where testosterone level had not been reduced significantly[36]. In a subsequent Phase Ⅰ/Ⅱ clinical trial, 13 patients with moderate to severe BPH were treated with a loading dose of 5 mg cetrorelix twice daily for 2 d and then with 1 mg daily for two months[42]. In this study, testosterone fell to castrate levels during the initial high dose therapy and increased to approximately 30% of the normal serum level during the 2 mo of maintenance therapy. On week 8, the International Prostate Symptom Score (IPSS) was significantly reduced and there was a 27% decline in prostate volume.

A decade after these pilot studies, a placebo-controlled phase II trial explored the effects of a 4-wk treatment at 3 different dose levels of cetrorelix in 140 patients with symptomatic BPH[43]. LUTS were significantly improved in all treatment groups compared to placebo which effect occurred rapidly, by week 4 (time point of the first evaluation). Prostate size was also significantly reduced in two of the treatment groups and the overall reduction of symptoms lasted 16 wk after the termination of the treatment (time point of last evaluation). In a further study, cetrorelix pamoate was administered as a 60 mg sustained release formulation, in a double-blind, randomized, multicenter study[44]. One subsequent administration of cetrorelix (30 mg, sustained release) resulted in a 4-point improvement in IPSS and the significant advancement was sustained for 26 wk after the last dose was given. In these latter studies it was shown that the suppression of testosterone levels by cetrorelix was moderate and transient[43,44].

Despite the success of these studies, the phase III clinical trials conducted in the United States and in Europe by AEterna Zentaris[45,46] failed to confirm a significant improvement in IPSS in response to cetrorelix treatment compared to the placebo group. In the United States study, there were no significant changes after either 3 or 4 doses of cetrorelix administered during an 18-wk period, however, cetrorelix was beneficial in a subgroup of patients with substantially enlarged prostates[47]. Although the phase Ⅲ trial failed, all previous attempts were successful which encouraged the initiation of new clinical testing with the more potent LHRH antagonist, degarelix. This compound has greatly reduced histamine-releasing activity and upon subcutaneous administration it aggregates into a slow-release complex[38,39]. A Phase-Ⅱ study has been completed with this compound but results have not yet been released[48].

Initially, the concept of the management of prostate cancer and BPH by LHRH antagonists was based on their action on pituitary LHRH receptors (LHRHR) leading to suppression of gonadal testosterone production, however, there is a growing body of evidence that they also act directly in the prostate. This idea is supported by a number of studies showing the presence of LHRH receptor in the prostate[49-51]. In an early study by Kadar *et al*[49], a high affinity low capacity binding site for D-TRP-6-LHRH in prostate samples from patients with BPH and prostate cancer was found. A similar binding site and one with low affinity high capacity were also detected in Dunning prostate tumors[50]. In a more recent study, LHRHR was detected by reverse transcription polymerase chain reaction in 60% of patients with BPH[51].

A second line of evidence for the local action of LHRH antagonists in the prostate is derived from a number of studies where cetrorelix was tested *in vitro* on human BPH cell lines expressing LHRHR. Siejka *et al*[21] showed that cetrorelix inhibits proliferation of the immortalized human BPH cell line (BPH-1) and reduces the protein expression of proliferating cell nuclear antigen (PCNA), epidermal growth factor (EGF), EGF receptor, most abundant adrenergic receptor in the prostate (α_{1A}AR) and LHRHR in a concentration-dependent manner[21]. Proliferation was also inhibited by cetrorelix after cells were stimulated with growth factors insulin-like growth factors (IGF)-Ⅰ, IGF-Ⅱ or FGF-2. Additionally, the activation of signal transducer and activator of transcription 3 (STAT3) by phosphorylation, an event associated with increased proliferation in many cells[52], was suppressed by cetrorelix[21]. The downregulation of $_{\alpha 1A}$AR by cetrorelix might be of particular interest since an increase in $_{\alpha 1A}$AR expression induced by prolonged administration of α1A-adrenergic blockers might be responsible for development

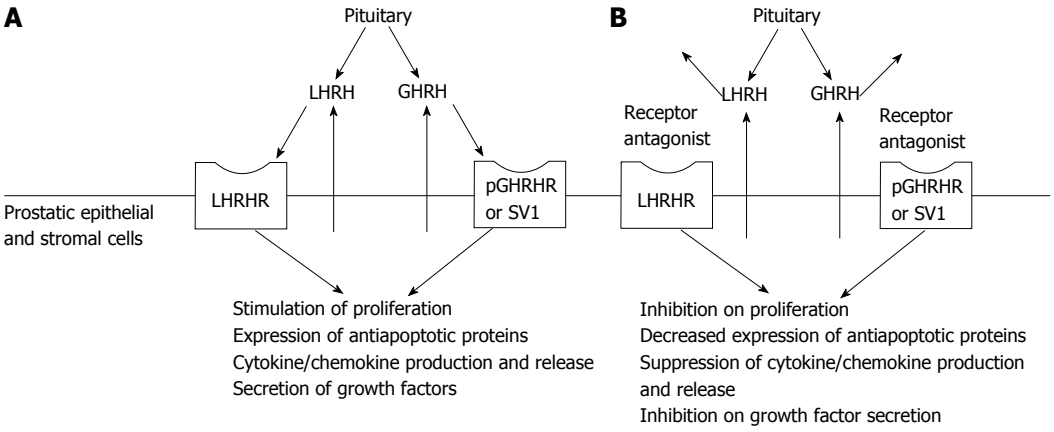

Figure 1 Local autoregulatory loop of luteinizing hormone-releasing hormone and growth hormone-releasing hormone in prostate cells and their blockade with antagonistic analogs: A novel strategy for the treatment of benign prostatic hyperplasia. A: Luteinizing hormone-releasing hormone (LHRH) secreted by pituitary somatotropes or by prostate cells activates local receptors (LHRHR). Similarly, pituitary-derived or paracrine/autocrine growth hormone-releasing hormone (GHRH) binds to pituitary type receptor (GHRHR) or its splice variant (SV1). These events lead to the changes in cellular homeostasis implicated in benign prostatic hyperplasia (BPH) pathophysiology; B: Disruption of the autoregulatory feedback loops by antagonists of LHRH and GHRH improves the condition of BPH by acting on these various cellular processes.

of the therapeutic tolerance to this treatment seen in clinical practice[53]. Rick *et al*[22] utilized a rat model of BPH in which the growth of prostate was induced by repeated administration of testosterone[54]. In this study, prostate size was reduced by cetrorelix in a dose-dependent manner compared to controls treated by testosterone only. In addition, the expression of various proinflammatory cytokines and growth factors that have been implicated in the pathogenesis of BPH were found to be reduced following cetrorelix treatment[22]. A significant reduction in serum levels of dihydrotestosterone and LH was also observed. Interestingly, cetrorelix treatment reversed testosterone-induced morphological changes to resemble the histology of the normal prostate, including a decrease in epithelial height[22]. In addition, AR and 5α-reductase levels were reduced by cetrorelix[22]. Unfortunately, the testosterone-induced BPH model has its limitations due to the complexity of the pathogenesis of BPH. Testosterone-induced hyperplasia selectively appears in the ventral prostate lobe in rats that might be the result of the distinct anatomy of this model from humans[55]. Also, the efficacy of testosterone to induce prostatic hyperplasia varies among different rat strains[56]. In addition to the noted disadvantages of the model, only the proliferation of epithelial cells is triggered by the addition of testosterone[56], whereas stromal-epithelial interactions are believed to be crucial in the pathogenesis of BPH[57,58]. Siejka *et al*[59] further examined this interaction using the BPH-1 cells and an immortalized stromal myofibroblast cell line, WPMY-1. Growth medium collected from either of the cell lines stimulated the growth of the other. This strongly supports the crucial role of epithelial-stromal cross-talk in the proliferative activity of these cells. This effect seemed to be directed through the mitogen-activated protein kinase (phosphorylation of ERK1/2) and STAT pathways. Cetrorelix inhibited the proliferation of both cell lines on its own and also after the BPH cells were stimulated with WPMY-1-conditioned medium[59].

The above mentioned studies shed light on the existence of a local autocrine/paracrine LHRH feedback in the prostate that might contribute to the pathogenesis of BPH (Figure 1). Since both LHRH ligand and its receptor are expressed in BPH[22] and the LHRH antagonist, cetrorelix, is able to decrease the proliferative activity of BPH cells *in vitro*[22], this feedback loop might act as a local stimulatory signal for cell proliferation or survival. It is also known that hormone-refractory prostate carcinomas express higher levels of LHRHR than BPH and hormone-dependent prostate cancer[60]. Consequently, LHRHR levels might gain prognostic value in the future.

GHRH ANTAGONISTS AND THEIR COMBINATION WITH LHRH ANALOGS

Antagonistic analogs of GHRH have been found to reduce the growth of various tumors[61-69] including prostate cancer in xenograft models of nude mice[70-74]. IGF-1 is a well-known growth-promoting factor for various tumors[70,75]. By blocking GHRH receptors on pituitary somatotropes, these antagonists suppress the production and secretion of growth hormone (GH) thereby decreasing circulating levels of IGF1. The full length pituitary type receptor (pGHRHR) and its main splice variant, splice variant 1, are expressed in various extrapituitary sites of normal and malignant tissues, including prostate[71,76,77]. GHRH is also secreted locally in normal and malignant prostate tissue, suggesting that it serves as an autocrine/paracrine regulator which process might be involved in the pathogenesis as well as the progression of prostate cancer[23,78,79]. Both *in vivo* tumor growth and *in vitro* cell proliferation are inhibited by GHRH antagonists in experimental androgen-dependent and-independent prostate cancers further indicating that, apart from their action in the pituitary, these peptides also function directly in the prostate[80].

Two studies have investigated the effect of GHRH antagonist monotherapy in experimental BPH models. They confirmed that both pGHRHR and GHRH are present in BPH-1 cells and in rat prostates[23,24]. Rick *et al*[23] reported also that the levels of pGHRHR and GHRH were increased following the induction of prostate growth by testosterone, indicating the importance of this autocrine/paracrine circuit in the pathogenesis of BPH (Figure 1). In the same study, GHRH antagonists were found to significantly reduce relative prostate weights better than finasteride, an 5-α reductase inhibitor. GHRH antagonists downregulated the mRNA and protein levels of various cytokines and growth factors that were elevated after testosterone treatment and also decreased proliferation and increased apoptosis in the prostate. GHRH antagonists decreased the transcriptional expression of growth hormones such as IGF-2, TGF-α, TGF-β1 and -β2, EGF, FGF-2, vascular endothelial growth factor (VEGF)-A, that have been found to contribute to the pathogenesis of BPH[81]. Cytokines interleukin (IL)-1α, IL-1β, IL-13, IL-15, and IL-17β, that have been downregulated by GHRH antagonists, otherwise promote T-lymphocyte infiltration and inflammation in BPH[82]. Interestingly, in this study, serum GH and IGF-1 levels were not affected significantly by the GHRH antagonist treatment, that might indicate the crucial role of their direct action in the prostate rather than through the pituitary axis. Intriguingly, prostates of testosterone-treated rats contained increased levels of the antiapoptotic molecule, B-cell lymphoma 2 (BCL-2), a process may explain the increased survival of cells implicated in the development of BPH[20]. Additionally, GHRH antagonist significantly dowregulated BCL-2 levels and simultaneously elevated the expression of the proapoptotic factor, BCL-2-associated X protein (BAX), and the tumor suppressor, p53, which events may underlie the strong apoptotic effect of these peptides.

In the study by Siejka *et al*[21] GHRH antagonists inhibited the proliferation of BPH-1 cells *in vitro*. The existence of the local GHRH/GHRHR loop was further supported by this study; incubation of the cells with GHRH resulted in an increased rate of proliferation which was then inhibited by the simultaneous addition of GHRH antagonist. Their study also revealed that GHRH triggers the phosphorylation of ERK 1/2, Janus kinase 2 (JAK2) and STAT3, signaling molecules that are known to be involved in the pathogenesis of BPH[83,84].

Since the existence of autocrine/paracrine systems of regulation by both LHRH and GHRH are strongly suggested in BPH, the simultaneous blockade of their receptors would be expected to result in a more effective therapy. Rick *et al*[85] studied the combination of cetrorelix plus a highly potent GHRH antagonist, JMR-132, in the testosterone-induced rat BPH model. They found that combination of LHRH and GHRH antagonists resulted in a greater decrease in prostate-specific antigen (PSA) and prostatic STEAP (six-transmembrane epithelial antigen of the prostate) protein levels than either of the peptides alone. Relative prostate weights were reduced to the control level by the combination therapy. Antagonists of GHRH and LHRH administered together were also more effective in inducing apoptosis as measured by changes in the levels of BCL-2, BAX, p53, nuclear factor (NF)-κB and cyclooxygenase-2 (COX-2). The combination therapy therefore has a great prospect in reducing hyperplastic prostate volume by triggering apoptotic cell death. In addition, chronic inflammation has been linked to the development and worsening of BPH; COX-2 has been proposed to play a key role in this process[86]. Hence, coadministration of GHRH and LHRH antagonists may also improve clinical outcome by reducing the expression of inflammation-related proteins such as NF-κB and COX-2[87]. In a subsequent study[88], the cumulative effect of cetrorelix plus JMR-132 was also superior to their individual inhibition on the proliferation of BPH-1 and WPMY-1 cells *in vitro*. Only the combination of JMR-132 and cetrorelix increased the proportion of cells in the S-phase significantly with a simultaneous decrease in the number of cells in G0/G1 and G2/M phases in BPH-1 cells. A decrease in the expression of several genes was detected in response to the combination treatment in the rat testosterone-induced BPH model; these included growth factors (EGF, FGF-1, -2, -7, -8 and -14, IGF-1 and-2, BMP5 and -7, VEGF-A, *etc*.), genes implicated in inflammatory response (chemokines, chemokine receptors, cytokines and cytokine receptors), and members of the Wnt, Hedgehog, PI3-kinase/AKT, JAK-STAT, Phospholipase C and low-density lipoprotein (LDL) pathways. According to the authors, among these changes, the downregulation of IGF-1 is of particular interest, since it has been linked to the development of BPH in diabetic men[89]. Also, inflammation-related chemokine/cytokine release has been shown to trigger the production of growth factors leading to the hyperplastic behavior of prostatic cells[90]. We therefore believe that combination therapy with antagonists of GHRH and LHRH might provide a highly beneficial approach to the management of BPH.

GRP

GRP is a bombesin-related hormone first isolated from porcine stomach and named for its ability to trigger the secretion of gastrin[91,92]. Among the three receptor subtypes that had been described for bombesin-like peptides, GRP binds to the first type (GRPR) with high affinity, and to the second type (neuromedin-B receptor) with a relatively low activity[93]. GRPR expression has been found in a variety of tissues where it regulates the secretion of gastric acid and stimulates exocrine function of the pancreas as well as triggering smooth muscle contraction in the stomach, gall bladder and urinary bladder[94,95]. In the prostate, GRP and bombesin have been shown to display mitogenic activity, affect cell migration and induce contraction in bladder and left ventral prostate[95,96]. In addition, GRPR has been implicated in the neurophysiology

of memory and fear-related behavior, and the processing of pruritus and penile reflexes[97]. In small-cell lung carcinoma xenografted into nude mice, an antibody against the GRPR receptor significantly inhibited tumor growth suggesting the crucial role of a GRP/GRPR autocrine/paracrine loop[98]. Soon after, the existence of this feedback regulation was demonstrated in various tumors, such as glioblastoma, colon cancer, hepatic cancer, prostate and gynecologic cancers[99-104]. Several antagonistic analogs that target GRPR have been synthetized by our group; among these RC-3940-Ⅱ possesses the highest affinity for GRPR combined with an increased antitumor efficacy[105].

GRPR is expressed in prostates from healthy patients as well as in those diagnosed with BPH and malignant prostate[106,107]. A study by Rick *et al*[25] using the testosterone-induced rat model, investigated the role of GRP/GRPR in BPH in greater depth. They demonstrated that GRPR and its ligand are expressed in prostates of normal as well as testosterone-induced rats and also in the human BPH-1 and WPMY-1 cell lines. A single high-affinity binding site was also identified, in control rat prostates and human cell lines, with a radioligand binding assay using ^{125}I-labeled [Tyr4]bombesin. In this study, the GRP antagonist, RC-3940-Ⅱ, inhibited the proliferation of BPH-1 and WPMY-1 cells *in vitro*. It also significantly decreased cell volume and triggered S-phase cell cycle arrest in these cells. The GRP antagonist dose-dependently decreased prostate size *in vivo* in testosterone-treated rats. The proteomic analysis of rat prostates revealed that treatment with RC-3940-Ⅱ reversed the testosterone-induced elevation in NF-κB phosphorylation and expression of androgen receptor and PCNA. Also, it decreased the mean epithelial area and induced apoptosis in testosterone-treated prostates. Analysis of the transcriptional changes in the different treatment groups identified several genes responsible for the beneficial effects of RC-3940-Ⅱ. Changes were found in the levels of growth factors, inflammatory chemokines, cytokines and their receptors; attempts to identify key signaling pathways for this process resulted in the implication of the Wnt, Hedgehog, TGF-β, NF-κB, JAK-STAT and LDL pathways. Accordingly, GRP antagonists may represent an important tool for the management of BPH, either alone or in combination with LHRH and/or GHRH antagonists.

POTENTIAL USE OF SOMATOSTATIN ANALOGS

Somatostatin inhibits the release of GH from the pituitary and also possesses inhibitory action in the gastrointestinal-tract and pancreas as shown by suppression of secretion of gastrin and glucagon, respectively[108,109]. There is much evidence that analogs of somatostatin can inhibit growth of various experimental tumors including prostate cancer[110]. Kadar *et al*[111] identified a single binding site for somatostatin using somatostatin analog RC-160 in rat prostate adenocarcinoma. In normal and pathologic prostate, findings deciphering the expression pattern of somatostatin receptors are contradictory. According to Dizeyi *et al*[112], among the five somatostatin subtypes (SSTRs), SSTR1-3 is expressed in the epithelium of normal and malignant prostate cancer, whereas SSTR4 was found only in epithelial cells. Specific neuroendocrine cells expressing SSTRs have also been identified. In a study by Tatoud *et al*[113], SSTR1 was found in most of the epithelial and stromal cell lines tested whereas SSTR2 was only detected in one BPH stromal cell line. By using fluorescent *in situ* hybridization techniques, SSTR4 mRNA expression was found only in the epithelium whereas SSTR2 was mainly detected in stromal cells of BPH and carcinoma[114]. Nevertheless, the expression of SSTRs in the prostate suggested that the use of somatostatin analogs in pathologic conditions of the prostate by inhibiting the autoregulatory loop of GHRH/GHRHR might be beneficial. In accord with this hypothesis, somatostatin analogs were shown to decrease the proliferation of androgen sensitive and androgen independent prostate cancer cells by elevating p27 and p21 protein levels, decreasing cyclin E expression and ERK1/2 phosphorylation and the secretion of IGF-1 and IGF-2[113,115,116]. The inhibitory activity of somatostatin analog on the production of growth factors, IGF-1 and IGF-2, is of particular interest since these powerful octapeptides have been linked to the pathogenesis of BPH[90].

Somatostatin analogs have also been tested clinically in patients with androgen-independent prostate cancer. A study by Maulard *et al*[117] showed improvement in PSA levels and achieved a reduction in bone pain. A Phase-I study demonstrated the favorable toxicity profile of somatostatin analog lanreotide, and showed its inhibitory effect on plasma IGF-1 levels. In contrast, no clinical improvement has been noted with this analog in advanced metastatic androgen-independent prostate cancer[118]. In a study by Berruti *et al*[119], lanreotide was also able to decrease plasma levels of IGF-1 and of the prognostic marker, chromogranin-A, but had no effect on serum PSA levels in patients with advanced prostate cancer. The poor or no inhibition of tumor growth to somatostatin analogs found in these clinical trials is thought to be due to differences in the receptor subtype-specific binding of the analogs. Consequently, the utilization of a non-receptor selective somatostatin analog has been suggested[120]. According to Cariaga-Martinez *et al*[121], whereas SSTR2 is expressed in benign prostatic hyperplasia, in most cases, it is repressed or absent in malignant prostate tissue. Conversely, the profound expression of somatostatin receptors in non-malignant prostate tissue indicates the need for preclinical and clinical testing of its analogs in BPH. This suggests that monotherapy with a somatostatin analog or a combination treatment with antagonists of GHRH and/or LHRH might represent a promising strategy for the treatment of BPH which should be investigated in the future.

CONCLUSION

The development of novel therapies for BPH is undoubtedly required. Whereas the beneficial effects of LHRH antagonists in pathological conditions of the prostate are already confirmed in clinical setting, other peptide analogs (antagonists of GHRH and GRP) have only been tested in experimental BPH models. We hope that the present review of findings on this topic will accelerate the further experimental and clinical investigation of these compounds. It appears that the local actions of various analogs in the prostate are more crucial for their beneficial influence on BPH than are their systemic effects on hormonal levels. By affecting the activation of multiple signaling pathways, LHRH, GHRH and GRP regulate cell cycle, apoptosis, cytokine and chemokine release as well as local immune response. Monotherapy or combination therapy with antagonists of LHRH, GHRH and GRP are suggested to represent an improved treatment compared to the currently available medical modalities.

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