

Targeting β -Arrestin for BPH Therapies

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Commentary

Benign prostatic hyperplasia (BPH) is a progressive disease in men over the age of 60 years characterized by non-malignant enlargement of the prostate [1]. Lower urinary tract symptoms associated with BPH can have a major impact on a patient's quality of life. Current therapies include those that block the alpha-adrenergic receptors (α -ARs), which are considered the first line drug treatment due to their rapid onset of action, good efficacy, and low rate and severity of adverse events [2]. Commonly used α -blockers include alfuzosin, tamsulosin, terazosin, and doxazosin. The rationale behind this therapy was based on the observation that prostatic muscle contraction results from the α -AR-mediated sympathetic stimulation. Therefore, α -blockers help relax the prostatic smooth muscle via the blockade of sympathetic α -AR [3]. As the α -AR subtypes are located differentially in the prostatic epithelium and stroma, the α 1-AR antagonists can act on both components. Currently, there is no complete cure for BPH and conventional drugs, including α -blockers, stand to gain from improved uroselectivity and reduced side effects.

In our recent paper in Biochemical and Biophysical Research Communications [4], we established an *in vitro* cell model for BPH utilizing BPH-1 cells and its pathophysiology via the ERK activation pathway with phenylephrine. Through this, we found that this pathway correlates with cell volume increase without affecting cell proliferation. Our study also reveals that the ERK pathway can be activated through α -AR effectors heterotrimeric G and β -Arrestin proteins. β -Arrestins are found to mediate ERK activation and to play a major role in the maintenance of cell volume change. β -Arrestins have been unexplored in the pathophysiology of BPH. Our findings suggest that β -Arrestins may serve as a novel target for future therapies. Additionally, we discovered that combinations of terazosin and tamsulosin or alfuzosin and doxazosin showed a synergistic and significant inhibition of both phenylephrine-induced ERK activity and cell volume increase when administered in a half dose concentration compared to their monotherapy. Terazosin and alfuzosin inhibit β -Arrestin-mediated ERK activation, while tamsulosin and doxazosin inhibit the G protein-mediated ERK activation. In clinical practice, this may suggest that certain combination therapies targeting α -AR can be utilized for further symptomatic improvement.

Other reports have demonstrated beneficial effects of other therapies in experimental models. Interestingly, gastrin releasing-peptide (GRP) antagonists have been shown to reduce the volume of human prostatic cells and lower prostate weight in an *in vitro* BPH model through their actions on prostatic GRP receptors [5]. Another study suggested that growth hormone-releasing hormone (GHRH) antagonists could be a useful experimental model of BPH and BPH therapy, possibly in combination with luteinizing hormone-releasing hormone (LHRH) antagonists [6]. These studies may suggest the

possibility of better therapeutic outcomes with the use of combination α -blockers (terazosin and tamsulosin or alfuzosin and doxazosin) in addition to other therapies, such as GRP antagonists or GNRH and LHRH antagonists, probably through synergistic inhibition of the β -Arrestin-dependent ERK activation. Further studies are warranted to demonstrate the clinical effectiveness of utilizing these combination therapies in BPH patients.

Clinical effectiveness of combination therapies of α -AR blockers alone are limitedly reported in literature. However, one review synthesized evidence from random controlled trials and observational studies where α -AR blockers, including tamsulosin, doxazosin, and alfuzosin, have been compared to and combined with various drugs. The review concluded that combination therapies tolterodine/ α -AR blocker, solifenacin/ α -AR blocker, and fesoterodine/ α -AR blocker have comparative effectiveness to α -AR blocker monotherapy and more adverse effects [7]. Another study revealed improved storage symptoms and quality of life when treated with fixed dose combination of α -AR blocker (tamsulosin) and antimuscarinic (solifenacin) blocker [8]. Yet, another study demonstrated phosphodiesterase 5 inhibitors combined with α -AR blockers had great improvement of lower urinary tract symptoms [9]. 5 α -reductase inhibitor has shown to reduce the dihydrotestosterone content of the prostate and significantly reduces prostate volume and BPH symptoms [10]. Current guidelines suggest the combination of α -AR blocker with 5 α -reductase inhibitor or muscarinic receptor antagonist can be used in patients with moderate-to-severe lower urinary tract symptoms [2].

While it is preferable for medical therapy to have various molecular targets, combination α -AR blockers were shown to have synergistic inhibition of the β -Arrestin-dependent ERK activation, and this can be further explored clinically. Furthermore, utilizing β -Arrestin can be a potential target for novel BPH therapies. It is unknown whether other therapies, such as 5 α -reductase inhibitor or muscarinic receptor antagonist have any effect on this molecular pathway. It is worth investigating the clinical benefit of synergistic inhibition of the β -Arrestin-dependent ERK activation and the effect of utilizing combination α -AR blockers compared to monotherapy in BPH patients.

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