Journal of Cell Signaling
ISSN: 2576-1471

Wang, et al., J Cell Signal 2016, 1:4

Commentry Open Access

Targeting β-Arrestin for BPH Therapies

Mindy Wang[1], Yehia Daaka[1] and Anindya Dey[2*]

[1]*Department of Anatomy and Cell Biology, University of Florida College of Medicine, Gainesville, Florida, USA*

[2]*Department of Obstetrics and Gynecology, Stephenson Cancer Center, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, USA*

[*]**Corresponding author:** Anindya Dey, Department of Obstetrics and Gynecology, Stephenson Cancer Center, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, USA, E-mail: Anindya-Dey@ouhsc.edu

Received date: Oct 05, 2016; **Accepted date:** Oct 19, 2016; **Published date:** Oct 26, 2016

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 α1-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 trails 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]. 5α-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 5α-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 5α-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.

References

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL (1984) The development of human benign prostatic hyperplasia with age. J Urol 132: 474-479.
2. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, et al. (2013) EAU Guidelines on the Treatment and Follow-up of Non-neurogenic Male Lower Urinary Tract Symptoms Including Benign Prostatic Obstruction. Eur Urol 64 : 118-140.
3. Debruyne FM (2000) Alpha blockers: are all created equal? Urology 56: 20-22.

4. Wang M, Daaka Y, Dey A (2016) Biased a-adrenergic receptor and ßarrestin signaling in a cell culture model of benign prostatic hyperplasia. Biochem Biophys Res Commun 471: 41-46.
5. Rick FG, Abi-Chaker A, Szalontay L, Perez R, Jaszberenyi M, et al. (2013) Shrinkage of experimental benign prostatic hyperplasia and reduction of prostatic cell volume by a gastrin-releasing peptide antagonist. Proc Natl Acad Sci U S A 110: 2617-2622.
6. Rick FG, Schally AV, Block NL, Abi-Chaker A, Krishan A (2013) Mechanisms of synergism between antagonists of growth hormone-releasing hormone and antagonists of luteinizing hormone-releasing hormone in shrinking experimental benign prostatic hyperplasia. Prostate 73: 873-883.
7. Brasure M, MacDonald R, Dahm P, Olson CM, Nelson VA, et al. (2016) Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: A Review.
8. **Dimitropoulos K, Gravas S (2015) Solifenacin/tamsulosin fixed-dose combination therapy to treat lower urinary tract symptoms in patients with benign prostatic hyperplasia. Drug Des Devel Ther 9: 1707-1716.**
9. Wang XH, Wang X, Shi MJ, Li S, Liu T, et al. (2015) Systematic review and meta-analysis on phosphodiesterase 5 inhibitors and α-adrenoceptor antagonists used alone or combined for treatment of LUTS due to BPH. Asian J Androl 17: 1022-1032.
10. Bartsch G, Rittmaster RS, Klocker H (2002) Dihydrotestosterone and the concept of 5alpha-reductase inhibition in human benign prostatic hyperplasia. World J Urol 19: 413-425.